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 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

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December 5, 2012
 1:30 p.m.

Holiday Inn
 2 Montgomery Village Avenue
 Gaithersburg, Maryland

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JOHN C. SOMBERG, M.D.	Voting Member
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AFTERNOON SESSION

(1:35 p.m.)

DR. YANCY: It is now 1:35, and I'd like to call this second session of this meeting to order of the Circulatory Systems Device Panel on today, December 5th, 2012.

Let me make our objectives for this afternoon clear. For this afternoon's agenda, the Panel will discuss and make recommendations regarding the 515(i) order for intra-aortic balloon and control systems, otherwise known as IABP by most of us, one of the remaining preamendment Class III devices that is predating 1975 approval by the 510(k) process, but at a Class III level.

Intra-aortic balloon pump systems consist of an inflatable balloon and a console which inflates in synchronization with the cardiac cycle. The discussions to be held this afternoon will involve making recommendations regarding regulatory classification, as we did earlier in the day, to either reconfirm to Class III or to reclassify intra-aortic balloon pumps to Class I or Class II.

Before we begin -- I would like to not do that. We already know who's at the table. With the exception of Dr. Ohman, we are as we were, so we can save a few minutes there. But I do think it's important that the FDA participants, within limits, introduce themselves. So, Matt, if we can start with you and go to your left, that'd be perfect. Introduction. Yeah,

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that's what you have here.

MR. HILLEBRENNER: Okay, then. Matthew Hillebrenner, Deputy Director, Division of Cardiovascular Devices.

DR. YANCY: Please.

MR. AGUEL: Fernando Aguel, Acting Senior Reviewer and Team Leader for the Circulatory Support Devices Branch.

DR. YANCY: And we've heard from Dr. Wu. Please.

MS. WENTZ: Catherine Wentz. I'm a lead reviewer for the Circulatory Support Devices Branch.

DR. YANCY: Thank you.

MS. RINALDI: Jean Rinaldi. I'm a biomedical engineer in the Office of Science and Engineering Laboratories.

DR. YANCY: Great. Thanks for still being here. Continue.

MS. BRANDA: I'm Rachel Evans. I'm a lead reviewer in the Structural Heart Devices Branch.

MR. CANOS: Daniel Canos, Branch Chief of the Division of Epidemiology.

DR. LASCHINGER: I'm John Laschinger. I'm a cardiac surgeon, medical officer, and physician in the Division of Cardiovascular Devices

DR. YANCY: Thank you.

DR. BROCKMAN: Randy Brockman, Acting Chief Medical Officer for the Office of Device Evaluation.

DR. YANCY: Great. I think that captures everyone. I don't see Dr. Pina, don't know if she's not back yet, but she'd be the only other person.

If you have not already done so, please make certain you've signed the attendance sheet.

And now Ms. Waterhouse, the Designated Federal Officer for the Circulatory System Devices Panel, will make some introductory remarks for the purpose of the record.

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. Code Section 208, Congress has authorized FDA to grant

waivers to 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 conflicts of interest.

Related to the discussion 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 intra-aortic balloon and control systems, one of the remaining preamendment Class III devices. Intra-aortic balloon pump systems consist of an inflatable balloon and a console which inflates in synchronization with the cardiac cycle. The discussion will involve making recommendations regarding regulatory classification to either reconfirm to 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 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 still do 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 that they may have with any firms at issue.

For the duration of the Circulatory System Devices Panel Meeting on December 5th, 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. The 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. Yancy, I would like to make a few general announcements.

Transcripts for today's meeting will be available from Free State Court Reporting, telephone number 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 in 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. Thank you very much.

DR. YANCY: Thank you, Ms. Waterhouse. Again, for the

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purposes of the record, let the record show that all of the members in attendance now represent the same group here earlier to discuss external counter-pulsating with the exception of Dr. Magnus Ohman.

It is approximately 1:45, and we are on time, and so we'd like to proceed with the FDA presentation, please.

MS. ULISNEY: Thank you. Good afternoon. My name is Karen Ulisney, and I'm the Lead Reviewer at FDA for intra-aortic balloon pump device classification.

You've heard from Marjorie and Dr. Wu this morning about the objectives of this meeting, and I think it's been repeated a few times since then. But we are here today to seek your recommendations regarding the classification of intra-aortic balloon pump devices' various intended uses. Balloon pump devices are one of the remaining preamendment Class III medical devices, and for Class III devices, premarket application, or PMA, is typically required. However, balloon pump devices are currently cleared and marketed through the 510(k) regulatory pathway, which is typically reserved for Class II devices.

The FDA will present the available clinical evidence to determine if there is sufficient evidence of device safety and effectiveness, risks associated with the use of balloon pump devices, and special controls to mitigate the risks to health. At the conclusion of this presentation, the Panel will be asked to weigh in on FDA's recommendations to either down-

classify balloon pump devices to Class II requiring 510(k)s or to keep them as Class III requiring PMAs.

The FDA team presenting with me today includes myself, Dr. Sansing, and Dr. Brooks. The content of our presentation is delineated here.

This outline represents the topics and order of our presentation. I'll begin with presenting the device definition and description, the regulatory history of balloon pump devices, and industry's response to the most recent 515(i) order, cleared indications for device use, and a discussion of risks to health associated with balloon pump device use. Dr. Sansing will then present the methodology of the literature, clinical literature review, and clinical evidence regarding device safety. And Dr. Brooks will present the clinical evidence regarding device effectiveness. And I will conclude with an overall summary of device safety and effectiveness and FDA recommendations for the regulation of balloon pump devices.

Balloon pump devices are regulated under 21 C.F.R. 870.3535 and are identified as a device that consists of an inflatable balloon which is placed in the aorta to improve cardiovascular functioning during certain life-threatening emergencies and a control system for regulating the inflation and deflation of the balloon. The control system, which monitors and is synchronized with the ECG, provides a means for setting the inflation and

deflation of the balloon with the cardiac cycle.

I will present the regulatory classification history in more detail later in this presentation.

The balloon pump system consists mainly of an inflatable balloon catheter and console, as Dr. Yancy mentioned in the introduction. Intra-aortic balloon pump counter-pulsation is performed with a polyethylene balloon mounted on a flexible catheter. The shaft of the balloon catheter contains two lumens. One allows for gas exchange from the console to the balloon, and the second lumen is used for catheter delivery over a guide wire for monitoring of central aortic pressure after placement. Insertion is generally performed via the femoral artery using a standard percutaneous technique over a guide wire provided with the balloon catheter and advanced to the descending aorta.

Following placement, the balloon catheter is connected to the console, which provides pneumatic flow of helium to the balloon to inflate and deflate in synchronization with the cardiac cycle. Software controls the inflation and deflation of the balloon based on the ECG and arterial pressure wave form to determine optimal timing.

The lumen of the catheter is connected to pressure tubing and a pressure transducer to allow for monitoring for central aortic pressure. Balloon pump therapy is performed on adult and pediatric patient in the inpatient critical care setting.

So you heard about the principles of counter-pulsation mechanics or mechanisms this morning during the ECP device presentation. Well, IABP devices have a very similar physiology internally. The goal of counter-pulsation therapy is to increase myocardial oxygen supply, decrease myocardial oxygen demand, and increase cardiac output.

The picture on the left of this slide depicts the rapid inflation in synchrony with aortic valve closure at the onset and throughout diastole to augment diastolic coronary perfusion pressure. This high pressure retrograde flow of blood to the aortic root increases the perfusion pressure of the coronary arteries, and coronary blood flow, thereby increasing myocardial oxygen supply.

The next picture depicts the rapid deflation at the onset of systole before the aortic valve opens, which decreases afterload, or what we consider the impedance to LV ejection, and left ventricular workload with subsequent decreased myocardial oxygen demand and increased cardiac output.

The totality of the hemodynamic effects achieved with counter-pulsation balloon therapy are listed on this slide. The result of these effects are clinically desirable and reach the treatment goal of increasing myocardial oxygen supply and decreasing myocardial oxygen demand to improve cardiac function and patient hemodynamics.

The regulatory classification history of balloon pump devices

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dates back to March 9th, 1979, when the panel recommended the classification of balloon pump devices as Class III requiring premarket approval. The panel believed at the time that there was insufficient medical and scientific information to establish a standard to assure the safety and effectiveness of the device. The panel went on to say that controversy exists as to whether the device is beneficial in many situations in which it is used and that it is difficult to use the device safely and effectively.

Risks to health identified by the panel will be discussed a little later in this presentation.

On February 5th, 1980, after receiving no comments on the proposed rule, FDA issued a final rule classifying balloon pump devices as Class III devices requiring premarket approval. Following the issuance of this final rule, FDA implemented a phased-in approach to regulating these devices. Of note, this regulation does not include specific indications for balloon pump use.

So more recently, April 9th, 2009, the 515(i) order was issued requesting balloon pump manufacturers to submit safety and effectiveness information to determine whether PMAs should be called for under its current classification, Class III regulation, or whether the FDA has sufficient evidence of safety and effectiveness and special controls can be established to mitigate the risks.

Four of five balloon pump device manufacturers responded.

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They collectively hold a total of 61% of all the cleared 510(k) devices. One manufacturer stated they were not aware of adequate and valid scientific evidence that would support reclassification of the device to a Class I or II, and three manufacturers recommended reclassification to Class III -- or excuse me -- to Class II.

All of the supporting information they provided is based on a review of the relevant clinical literature, preclinical and clinical testing, and 40 or more years of information and knowledge about the clinical use of these devices.

As I mentioned earlier, the current regulation does not include specific indications for balloon pump use. We have grouped the cleared indications for use into several broad categories to facilitate the summary of the literature. The categories are acute coronary syndrome, or ACS, cardiac and non-cardiac surgery, complications of heart failure of both ischemic and non-ischemic etiologies, and septic shock and intraoperative pulsatile flow generation.

As you can see from this slide, the indications under each category are numerous. Since the first reported clinical use of a balloon pump in 1968, the cleared indications have evolved over the last several decades. Initially, balloon pump was developed to provide circulatory support in established cardiac decompensation that was considered reversible, such as failure to wean from cardiopulmonary bypass support

following cardiac surgery.

Indications expanded with clinical utility for various disease states, such as to provide hemodynamic support from imbalances of coronary supply and metabolic demand. The 510(k) process requires a demonstration of substantial equivalence to the predicate device. And for balloon pump devices, this has not included the evaluation of clinical data. FDA review of indications for use have evolved over time in terms of what they mean and how the FDA has regulated them.

In the case of inadequate cardiac function and failing circulation, IABP can obviate the need or delay the need for more invasive alternative mechanical circulatory support systems, such as ventricular-assist devices as a bridge to definitive treatment.

FDA is proposing these three main groups of indications, ACS, cardiac and non-cardiac surgery, and complications of heart failure to be down-classified to Class II indications. Other uses, including septic shock and intraoperative pulsatile flow generation, or IPFG, remain Class III indications due to the paucity of information to provide sufficient evidence of safety and effectiveness.

The original panel, in 1979, identified the risks to health listed on the left side of this slide. Cardiac arrhythmias, ineffective cardiac assist, thromboembolism, aortic rupture or dissection, limb ischemia, gas embolism and hemolysis. FDA believes that these risks are still relevant for balloon

pump devices today.

Additional risks to health are listed on the right side of this slide. These are risks identified by manufacturers and duplicated in the FDA MAUDE, or adverse event database search. They include infection, insertion site bleeding, leaks of the membrane or catheter, balloon entrapment, insertion difficulty, failure of the balloon to unwrap, malposition, vessel occlusion, and thrombocytopenia.

Special controls can be used to mitigate the risks to health for the Class II indications we are recommending. Experience with this device over many years of use informs the special controls we will discuss later in this presentation.

We also want to advise the Panel that all balloon pump devices currently have the following contraindications as part of their labeling, and these should be considered as part of the risks to health discussion as well as potential risk mitigations.

So the clinical evidence used to evaluate the safety and effectiveness of balloon pump devices is primarily found in the FDA medical device-related adverse event reporting, or MDR reports, and review of the published literature, which Dr. Sansing and Dr. Brooks will provide.

As mentioned earlier, balloon pumps have been cleared for use under the 510(k) pathway and did not include IDE studies or postmarket surveillance studies.

Can you see that fairly well? Perhaps maybe -- okay, I know you have a front-row seat, so that's probably best. I do apologize if it's difficult, but perhaps in your handouts you'll be able to see it, but I will reference specific numbers.

DR. YANCY: It is slide 18 in our presentations at our position.

MS. ULISNEY: Thank you.

This table provides a summary of the balloon pump MDR events from January 1st, 2002 to November 1st, 2012, related to death, injury, and device malfunction. A total of 5,493 events were reported with balloon pump devices over this 10-year period. Averaging the data over the 10-year period, which would be the far column on the right, divided by 10, there were 19 deaths, 180 injuries, and 345 device malfunctions per year.

Critical factors to consider as part of a benefit/risk assessment is the intended population is a group of patients with high morbidity and mortality, so deaths and injury are more reflective of the critically ill population.

The top-reported device malfunctions were balloon leak, balloon rupture, and air leak.

To put this table somewhat in perspective, there are many limitations to the evaluation of data from MDR reports; this was discussed a bit this morning. They provide a qualitative look at events and event rates. The information reported is most often insufficient to make judgments

about causality and the true frequency of adverse events related to device use. MDR reporting to the FDA is voluntary, so not all events are captured. Additionally, the denominator for event rate is not reported and can be difficult to ascertain from manufacturers.

The most up-to-date information we have on balloon pump procedures is from the National Center for Health Statistics in 2002, when an estimated 42,000 patients received balloon pump therapy in the United States.

The shaded area to the top right of your slide, we took a look at a review of the 81 deaths. So if you add the years of 2010 to 2012, we took a more focused look at those 81 deaths, which revealed that only three deaths, or 3.7% of the reported deaths, for a rate of 1 per year, were directly attributed to the device by either the operator in review of the MDR report, the operator declaration of that, or our FDA reviewers. One of these was the result of a self-reported poor operator technique causing vascular trauma and bleeding in a critically ill patient. A further 12.3% had insufficient information reported to correctly attribute the death to balloon pump or any other direct cause. This leaves 81.5% of the reported deaths as not attributable to the balloon pump, but instead to the comorbid conditions of these critically ill patients despite a balloon pump mechanical failure.

At this time, I would like to introduce Dr. Veronica Sansing,

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who will present the methodology of the literature review and safety data for the proposed Class II indications for balloon pump use.

DR. SANSING: Thank you, Karen.

I'm Dr. Veronica Sansing. I'm the epidemiologist and team leader for the Cardiovascular Branch of the Division of Epidemiology.

The objective of this part of the literature review was to assess the safety of the intra-aortic balloon pumps. I will present the methods, the findings, the overview of the published literature in regards to safety and a discussion of the strengths and limitations. This will be followed by a conclusion.

PubMed and Embase were searched using the following terms: intra-aortic balloon pumps, evidence for safety, and the following terms for the proposed Class II and Class III indications for use. The timeframe spanned from January 1st, 1975 to September 1st, 2012. The articles were limited to English publications.

We first identified records within Embase and PubMed. Of these articles, 282 articles were excluded for the following reasons: All research articles were included, but we excluded case reports and case series with less than 10 patients. Articles that were included in the qualitative review resulted in 34. Of these, there were 34 which were for the proposed Class II indications for use and 3 for the proposed Class III indications for use.

For the purposes of this safety review presented today, articles were considered for a consideration for inclusion if they were published after the year 2000, constituting modern versions of the IABP and smaller diameters placed percutaneously and reflective of currently cleared indications in the intended use populations.

Of the 34 articles for the proposed Class II indications for use, there were 20 cohort studies, four randomized controlled trials, three case controlled studies, two case series, four systematic reviews, and one meta-analysis. The study populations were conducted in the U.S., Europe, and Asia. Sample size ranged from 6 to 181,599 subjects.

What is evidence of safety for IABP for the proposed Class II indications for use? This includes acute coronary syndrome, cardiac and non-cardiac surgery, and complications of heart failure of ischemic and non-ischemic etiologies.

When interpreting the results related to the systematic review of safety, there are several factors to consider. Most studies examined multiple indications for use. Therefore, stratifying the results by a specific indication was limited. The definition of clinical endpoints may vary from study to study. Some studies examined comparative safety in these events. The literature review focused only on the patients who received IABP. Several studies reported the rate of adverse events at multiple time points. Therefore, both the proportion of patients with the adverse events and the

rate of the adverse events are reported. Patient demographics and risk profiles can vary from study to study, thereby creating a wide range of adverse events reported.

Based on primary studies that examined specific indications for use, the most commonly studied indications for use were: support of patients in cardiogenic shock and patients presenting with acute MI; support for diagnostic percutaneous revascularization and interventional procedures such as angioplasty or stent in diseases such as atherosclerotic coronary artery disease facilitated by IABP placement; prophylactic support in preparation for cardiac surgery; post-surgical myocardial dysfunction/low cardiac output syndrome; and support for complications from heart failure; mechanical bridge to other assist devices and cardiac support following correction of anatomical defects.

We compiled a list of the most frequently reported adverse events. They include mortality, bleeding at access site, and femoral artery occlusion. Mortality rates in patients in which IABP is utilized is generally high, reflecting the clinical status of the patient. In two studies which examined the Benchmark Registry, death was directly attributed to IABP or IABP placement in less than .05% of patients. Bleeding at the access site ranged from .06% to 4.3% at less than 6 months. This occurred in two studies. The incidence of femoral artery occlusion ranged from .1% to 3%. Neither study specified a time after insertion. 3% of patients experienced

femoral artery occlusion in the smaller study of 135 patients. The low incidence of .1% is from patients in the National Cardiovascular Data Registry.

The most frequent adverse events also include renal failure, infection, and hemorrhagic stroke. No study could establish a direct relationship between renal failure and IABP use. The rate of infection ranged from 0% to 9.6% in the timeframe of less than 6 months. A single study presented a rate of infection of 9.6% in patients undergoing cardiac surgery who required IABP. When focusing on the larger registry studies, the observed rates ranged from .1% to .7%. For the one study in which no time to event was specified, there were no reports of hemorrhagic stroke.

For events reported at less than 6 months, the rates ranged from 0% to 2.6%. Hemorrhagic stroke may have resulted from anti-coagulant use necessitated by the use of IABP. But studies did not report whether the patients had other simultaneous indications for anticoagulant use independent of the IABP or whether other agents, such as antiplatelet medications, may have contributed to the rates observed.

Other adverse events reported included vascular complications, including those listed here. The range was 5.9% to 13.7% at less than 6 months; amputation of .1% at greater than 6 months; and visceral thrombus at .1% at 6 to 12 months.

There are several limitations to this portion of the literature

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review. It is of note that the focus of this portion of the literature review was the phrase intra-aortic balloon pump and did not include studies that did not utilize this term.

The main limitation of this review is its inability to determine a definitive association between IABP use and the adverse events. Not all of the studies were designed to describe the adverse events associated with IABP. Most of the studies in the literature review face selection bias given the patient populations were selected to assess device performance in various patient populations. Articles which examined multiple indications for use did not stratify the adverse events by the indications for use. Therefore, the review cannot present the adverse events that occur within the specific indications for use for every article.

The robustness of the sample size varied. The sample size per indications for use could range from 6 patients to greater than 100,000 patients. Therefore, a high proportion of adverse events could range from a small denominator while a small proportion could be the result of a large denominator.

The most common limitation was a small sample size in 21 articles, no randomization in 7 articles, and a single-site design in 3 articles.

Some articles were based on a single-site study while others were based on multiple sites. Single-site studies, while providing a homogenous patient population resulting in increased internal validity, can

sometimes be biased because the data may not be influenced -- may be influenced by the practice of the institution, and the external validity is decreased.

In conclusion, results from the literature review demonstrate low overall rates of complications. The patients in whom IABP is implanted have severe comorbidities and underlying illnesses. As a result, overall mortality in these patients is high. It is difficult to discern whether the assessed mortality or adverse event data relates to the device or the surgical procedure or the patient population.

Overall, there is sufficient evidence for a conclusion of device safety with more recent data to be presented by Dr. Brooks in the next section of this presentation.

DR. BROOKS: Thank you, Dr. Sansing.

My name is Steven Brooks. I'm an interventional cardiologist and a medical officer at the FDA. I will review the data which supports intra-aortic balloon pump usage.

The intra-aortic balloon pump was first invented in 1962 and first used in humans in 1968. At that time, the device was 12 French in size and was inserted surgically via a vascular cut-down through a Dacron graft sewn to the femoral artery. Many were placed via the transthoracic approach, through a midline thoracotomy at the time of coronary artery bypass surgery. Since that time, the devices have decreased in size to

7 French and are placed percutaneously.

Safety has increased with each generation culminating in the low event rates described by Dr. Sansing. The literature, which has supported balloon pump, has similarly evolved. Original studies in the 1960s describe the hemodynamic effects of balloon pump use. These principles were applied to clinical scenarios in which these hemodynamic effects would be beneficial. And the devices were then used.

Case series of balloon pump use and various clinical indications were published, and this served as the burden of evidence at that time. The threshold of evidence required to support a change in the standard of care at that time was low. On this basis, the device was recognized by thought leaders and professional organizations as the standard of care. It wasn't until the 1990s that the first large modern trials were conducted to systematically test safety and effectiveness.

The full device literature was searched. And the evidence for device effectiveness was considered based on currently cleared indications. The FDA has grouped these indications into four broad categories, as noted in this slide: acute coronary syndrome; cardiac and non-cardiac surgery; complications of heart failure, both ischemic and non-ischemic etiologies; and septic shock and intraoperative pulsatile flow generation, IPFG.

Applicable literature is subsequently discussed regarding the available effectiveness information for each broad categories. The first of

these categories, acute coronary syndrome, has the most robust evidence to support effectiveness of the balloon pump. The literature can be further divided into four categories.

The earliest studies had demonstrated the mechanism of action in ACS whereby coronary blood flow is increased during diastole, myocardial oxygen demand is decreased by the hemodynamic effects of the device, mainly afterload reduction.

The first group of studies to demonstrate positive outcomes were observational studies such as registries which noted patient characteristics and outcomes among cohorts of patients who received treatment with balloon pump.

In the 1990s, the balloon pump was studied in the setting of infarct cardiogenic shock and fibrinolysis. These trials demonstrated positive outcomes and supported the mechanism of action and its utility as a tool in the treatment of ischemia and cardiogenic shock.

The final group of studies are those that have occurred in the modern era of emergent revascularization with PCI. The role of balloon pump here is one of an adjunctive therapy among multiple, concurrent therapies, each with increased efficacy over previous eras. These trials have shown both positive and negative benefits.

The first data supporting balloon pump use in ACS with cardiogenic shock came from observational or registry studies. The

Benchmark Registry was an international balloon pump registry of Datascope patients from 1996 to 2001 which enrolled 19,636 U.S. and 3,027 O.U.S. patients. Mortality of patients with cardiogenic shock was 30.7%, which was low compared to other cardiogenic shock trials and has been cited as evidence for benefit from balloon pump use.

Further evaluation of this registry has shown that in U.S. patients compared to O.U.S. patients, the balloon pump was placed at earlier stages of the disease and presentation. After appropriate adjustment of risk factors, U.S. patients showed decreased mortality, 10.8% versus 18% O.U.S., with a p-value of less than .001.

The results of the GUSTO-1 trial also demonstrated a 12-month survival advantage in cardiogenic shock with early balloon pump implantation. This was a retrospective study of balloon pump use in patients presenting with acute MI and cardiogenic shock who received systemic fibrinolysis. Sixty-eight of 310 cardiogenic shock patients received a balloon pump. The significantly higher frequency of balloon pump use in the U.S. in relation to Europe in these two trials was associated with more bleeding complications but also with a lower mortality rate, both nonsignificantly at 30 days in this trial, 47% versus 60%, and significantly at one year, at 57% versus 67%.

The NRMI-2 Registry was described in two publications which are relevant to balloon pump. Chen et al. analyzed data from 12,730

patients from 1994 to 1998. Hospitals were stratified into three groups by their annual number of balloon pump implantations. The mortality rate at these centers due to acute MI with complicating cardiogenic shock decreased depending on the frequency of balloon pump placement from 65.4% at low frequency sites to 54.1 and 50.6 at higher frequency sites. Multivariate analysis show that high balloon pump placement rates were an independent predictor of lower mortality.

A second publication from NRM-2 by Barron et al. examined the effect of balloon pump in infarct-related cardiogenic shock patients. Of 23,180 patients with ischemic cardiogenic shock, 24% received systemic fibrinolysis, and 12% were treated by angioplasty. The multivariate analysis showed that under these conditions, balloon pump treatment was associated with an 18% reduction in hospital mortality.

The first important study in the next group of trials, the fibrinolysis trials and acute MI, was the TACTICS trial. This was a prospective, randomized trial, balloon pump, in patients with acute MI, hypotension, and suspected cardiogenic shock treated with systemic fibrinolysis. The study was terminated early due to slow enrollment after 57 patients, 30 of whom received a balloon pump. No significant difference in mortality was detectable in the overall population of patients at 30 days, 27% versus 33%, or at 6 months, 34% versus 43%, although nonsignificant trends toward improvement were seen.

There was an observed mortality benefit seen in the subgroup of patients with Killip Class III and IV presentation, at 39% versus 80%, which reached statistical significance. This was not the primary endpoint of this trial and so must be considered with caution.

Waksman et al. reported the outcomes of patients presenting with acute MI and cardiogenic shock treated by fibrinolysis. In-hospital survival in the 24 patients with cardiogenic shock treated with balloon pump was significantly improved compared to 21 similar patients not given balloon pump, 46% versus 19%. Although there was a high rate of revascularization in the former group, they had survival rates similar to historical control subjects who did not undergo revascularization.

The SHOCK Registry included 251 patients presenting with acute MI complicated by cardiogenic shock from 1992 to 1993. In patients treated with balloon pump, survival was significantly improved, 43% compared with 28% without balloon pump. However, patients with balloon pump were significantly younger, 64.5 versus 68.2 years, and more often underwent cardiac catheterization, 88% in the balloon pump group versus 30% without balloon pumps.

After adjusting for cardiac catheterization status, there was no significant association between mortality and balloon pump use. Among 47 patients who underwent angioplasty, mortality rates did not differ significantly by balloon pump use, 62% in the balloon pump group versus

54% without it. The success rates of angioplasty were also similar for patients with and without balloon pump, 69 versus 60%.

The next group of trials occurred in the modern era of emergent PCI for acute MI. The IABP SHOCK trial randomized 45 consecutive patients enrolled from March 2003 to June 2004 who presented with acute MI and cardiogenic shock undergoing PCI to balloon pump in 19 patients or no balloon pump in 21 patients. Neither the primary endpoint, serial APACHE II scoring during the first four days, nor the 28-day mortality, 36.8% in the balloon pump group and 28.6% in the no balloon pump group, were significantly different.

The study did demonstrate improvement in hemodynamics, which did not reach statistical significance, including reduction in APACHE II score as a marker of severity of disease, improvement of cardiac index, reduction of inflammatory state and reduction of BMP biomarker status compared with medical therapy alone, but it did not demonstrate a decrease in morbidity or mortality. The study is limited by its small sample size.

The CRISP AMI trial was a randomized controlled trial of patients with anterior ST elevation, myocardial infarction without cardiogenic shock, who were randomized to balloon pump versus no balloon pump therapy, with treatment for up to 12 hours -- for a minimum of 12 hours in the balloon pump group.

This study enrolled 337 patients from June 2009 to February

2011. The primary endpoint was a reduction in infarct size as a percentage of left ventricular mass and was measured by MRI at 5 to 7 days. The trial found that infarct size was not significantly reduced and there was no significant difference in major and minor bleeding events between the two groups.

An exploratory composite endpoint of time-to-death, cardiogenic shock, or new or worsening congestive heart failure was significantly improved in the balloon pump group, with 8 events in this group, for a 5% incidence, versus 21 events, or a 12% incidence, $p=.03$, in the no balloon pump group. This positive result was driven by no shock noted in any of the balloon pump patients.

There are some qualifications or concerns regarding this study, and these include, one, the large crossover in the control group, in which 15 patients in the no balloon pump group crossed over to the balloon pump group. This may have biased the results. Additionally, the duration of treatment was different. As we'll discuss, in these modern trials with PCI and open vessel, the greatest intervention is the opening of the vessel, and the additive effect of balloon pump support may be less than in previous eras without open vessel.

The time to device in this trial, from door to first device placement, was 77 minutes in the balloon pump group and 68 minutes in the no balloon pump group. This was a difference of 9 minutes where over-

opening of the artery where these patients were supported by balloon pump, and this difference may not have been long enough to see a beneficial clinical outcome. So that's a qualification of this trial.

The IABP SHOCK II trial, published in October 2012, randomized 600 patients presenting with acute MI to cardiogenic shock to either balloon pump in 301 patients or no balloon pump in 299 patients; 277 patients underwent early revascularization. At 30 days, 119 patients in the balloon pump group, or 39.7%, and 123 patients in the control group, 41.3%, had died, a non-significant difference. There were no significant differences in secondary endpoints or in process-of-care measures, including the time to hemodynamic stabilization, the length of stay in the intensive care unit, serum lactate levels, the dose and duration of catecholamine therapy, and renal function.

The rates of adverse events were not significantly different between the groups. It is notable that 37 patients, or 13.4%, had the balloon pump inserted before revascularization, and 240 patients, or 86.6%, had the balloon pump inserted after revascularization, which may have affected the effectiveness endpoints. There was no significant difference in mortality between these two groups of patients with differences in balloon pump timing; mortality of 36.4 in the group with the balloon pump placed before revascularization and 36.8 afterwards. However, the difference in the timing of treatment cannot be separated from the patient demographics

or comorbidities which may have led to differences in the timing of treatment between these two groups. This could have confounded the results, making them difficult to interpret.

In summary, early studies of balloon pump demonstrated improved hemodynamics and augmented coronary blood flow, supporting the purported mechanism by which balloon pump would improve outcomes in ischemia. In early data from trials of acute MI complicated by cardiogenic shock and treated by fibrinolysis, balloon pump treatment demonstrated improvement in mortality.

In more recent trials of this patient population treated by earlier revascularization using PCI as opposed to fibrinolysis, balloon pump treatment may have a reduced incremental benefit. Trials performed to investigate the benefit of balloon pump using the modern standard of care have been underpowered to demonstrate improvement or have had other limitations such as variability in the timing of balloon pump usage.

The incremental benefit of balloon pump in the setting of early revascularization may be relatively less than in prior eras, which had a lower standard of care and less effective primary and adjunctive therapies.

On the basis of evidence from these studies, the 2004 ACC/AHA Guidelines for ST elevation MI and the 2011 ACCF/AHA/SCAI Guidelines for PCI recommend the use of balloon pump for hypotension, low output state, cardiogenic shock, and mechanical support of the failing heart

in the setting of acute MI as a Class I indication, level of evidence B.

The second broad category of cleared indications for balloon pump uses is in cardiac and non-cardiac surgery. The first uses in this category were for hemodynamic support of patients undergoing cardiac surgery who failed to wean from cardiopulmonary bypass. This has been termed postcardiotomy low cardiac output syndrome, or LCOS, and it's been seen in 2 to 9% of patients undergoing open heart surgery and is associated with increased hospital mortality, morbidity, and costs.

Multiple studies have looked at strategies to prevent or mitigate this, with conflicting results. The principles and successes in this realm were subsequently expanded and applied prophylactically to patients preop for cardiac surgery and then for non-cardiac surgery.

Christenson et al. randomized 30 high-risk off-pump bypass patients to receive either IABP preoperatively or no balloon pump. The use of the balloon pump improved preop and postop cardiac performance significantly, as well as the postop course, including decreased pneumonia and acute renal failure, shorter duration of ventilator support and fewer patients requiring postop inotropic medications. The lengths of stay in the ICU and in the hospital were shorter in the balloon pump group.

Miceli et al. studied 141 consecutive patients from 2004 to 2007 undergoing CABG. 27% of patients received prophylactic balloon pump. After risk adjusting for propensity score, prophylactic balloon pump

patients had a significantly lower incidence of postcardiotomy low cardiac output symptom and postop myocardial infarction, as well as a shorter length of hospital stay, 10.4 versus 12.2 days, compared to those who did not receive balloon pump.

Other studies have demonstrated a mixed or no benefit. Baskett et al. reported no evidence of benefit of preop balloon pump insertion, with a higher in-hospital mortality. These results may be due to a very high proportion of urgent operations.

Holman et al. excluded patients receiving preop balloon pump from hemodynamic instability, recent MI within 3 days of bypass surgery, or those undergoing emergent operations. They did not find any survival advantage for patients who received a prophylactic balloon pump insertion compared to risk-matched controlled patients, showing only a shorter, post-CABG length of hospital stay.

A meta-analysis by Field et al. of five randomized clinical trials included 105 patients treated prophylactically with balloon pump and 88 control patients. The authors concluded that available evidence suggests the preop intra-aortic balloon pump may have a beneficial effect on mortality and morbidity in specific high-risk patient groups undergoing bypass surgery. However, the randomized evidence is from a number of small trials with a high proportion of unstable patients recruited at a single institution.

The literature for balloon pump in non-cardiac surgery is less robust. There were no randomized trials found. Most were case series with limited patient numbers. Siu et al. noted no evidence of perioperative MI while the balloon pump was in place in their case series, and Grotz and Yeston also noted good results in their patients treated prophylactically with balloon pump during non-cardiac surgery.

Another indication related to cardiac and non-cardiac surgery is balloon pump use as a bridge to either assist devices or transplantation. Norkiene et al. studied 11 adult patients with decompensated dilated cardiomyopathy listed for heart transplant who were recorded in the Benchmark Registry from 2004 to 2005, with New York Heart Association Class IV functional status.

After 48 hours of intra-aortic balloon pump support, there was a significant increase of mean systemic arterial pressure from 74.5 to 82.3 mmHg and ejection fraction from 14.7% to 21%. Improvement of the cardiac index, pulmonary capillary wedge pressure, and end-organ perfusion markers did not reach statistical significance. The authors concluded that intra-aortic balloon pump support may be successfully and safely used in the acute decompensated dilated cardiomyopathy patients as an urgent measure of cardiac support to stabilize the patient and maintain organ perfusion until transplant is available, ventricular assist devices are placed, or the patient is weaned from balloon pump.

In summary, the literature regarding the effectiveness of balloon pump in cardiac and non-cardiac surgery is conflicting, with some studies demonstrating utilities and others which are equivocal or fail to demonstrate effectiveness. Demonstrating utility represents a challenge of clinical trial design, with well-executed trials, free of crossover and bias, with carefully chosen patient selection criterion endpoints. Given the benefit demonstrated in some such trials, it is clear that certain groups of patients with specific clinical indicators and features of surgical risk may benefit from balloon pump use for this group of indications.

The balloon pump was the first mechanical treatment available for congestive heart failure. Prior to its introduction in 1968, the only available therapies were inotropic agents, vasopressors, and diuretics. Studies in animals and humans had demonstrated the hemodynamic signature of the device.

Kantrowitz et al. published the first clinical data balloon pump therapy in patients with cardiogenic shock in 1968. He reported on two patients with cardiogenic shock who, after a balloon pump was inserted by arterial cut-down, showed improved arterial and central venous pressures and increased urine output.

In 1980 Bregman described percutaneous insertion with increased safety.

The series published by Norkiene et al. detailed earlier

documents the hemodynamic effects observed in a target population with dilated cardiomyopathy awaiting transplant, an analogous population in device indication.

Rosenbaum et al. studied 43 patients with end-stage congestive heart failure in whom the balloon pump was used as a bridge to transplant. Twenty-seven patients had non-ischemic cardiomyopathy, and 16 had ischemic cardiomyopathy. Hemodynamics improved significantly in both groups immediately, within 15 to 30 minutes following balloon pump insertion, with greater improvement in cardiac index and a trend toward greater reduction and filling pressures in the non-ischemic cardiomyopathy group. Systemic vascular resistance fell to a similar degree in both groups. All hemodynamic changes persisted in both groups with continued balloon pump support. The reduction in filling pressures, however, tended to be greater in patients with ischemic cardiomyopathy. Complications were low.

The authors concluded that balloon pump use was both safe and effective in this group as a bridge to transplant.

In summary, most of the larger studies demonstrating survival benefit in cardiogenic shock come in patients with cardiogenic shock from acute MI, as detailed earlier. There are data in smaller series of patients in heart failure, including indications such as bridge to transplant, children awaiting transplant, and acute decompensated dilated cardiomyopathy.

Given the device's mechanism of action, the measured

hemodynamic benefits, and the known safety profile, the device has been used ubiquitously over the last 45 years to support cardiac mechanics and hemodynamics in physiologic states consistent with the balloon pump's mechanism of action while the heart recovers or the patients is optimized for the next therapeutic treatment.

Clinical practice and expert consensus has followed from this evolution of the device use, and the balloon pump is accepted as effective based on this background and the prolonged history of use. It is considered to be one therapeutic intervention among many used in a multifactorial approach to hemodynamic support in these sick patients.

A final group of cleared indications for balloon pump exists which does not fall under the three categories described previously. These indications are not supported by sufficient safety and effectiveness data, and FDA will ask the Panel to consider that these other indications be classified as Class III indications. Currently, the indications of septic shock and intraoperative pulsatile flow generation would fall under this heading.

The hemodynamic effects generated by the balloon pump do not address the fundamental hemodynamic derangements of the septic shock syndrome. In fact, currently approved labeling lists septic shock as a contraindication to safe balloon pump use. No articles regarding the safety or effectiveness of balloon pump for septic shock in humans were found through the systematic literature search. A single study in swine failed to

demonstrate improved hemodynamics in support of this assertion.

Therefore, the safety and effectiveness of balloon pump for septic shock in humans cannot be systematically determined from the published literature. The device has no theoretical or literature-demonstrated utility in this clinical syndrome.

The use of the balloon pump for intraoperative pulsatile flow generation within all indications for use from our systematic literature search was less than 1%. Within the entire Benchmark Registry, less than 1% to less than 4.2% of the IFUs, or indications for use, were in the composite category of "not indicated; miscellaneous or other (intraoperative pulsatile flow)."

The indication of IPFG here may actually reflect a difference in terminology, with the term IPFG referring to the hemodynamic mechanism of action of the balloon pump rather than a desire to specifically generate pulsatile flow as compared to continuous flow. Balloon pump use for IPFG, therefore, makes up a small percentage of the overall use of balloon pump within the past two decades. This may account for the limited publications regarding this indication.

Three observational studies, including two with data from the Benchmark Registry, provided no conclusive evidence for safety or effectiveness for IPFG use. All three articles state that the device is associated with low mortality and low adverse event rates. However, since

no article stratified mortality by indication, these safety results do not apply specifically to the indication of IPFG.

With the development and increased use of continuous flow ventricular assist devices, comparative studies have failed to observe a difference in hemodynamic surrogates, clinical outcomes, or neurocognition with the use of pulsatile flow compared to continuous flow. This is directly applicable to the balloon pump indication of IPFG. All other mechanistic and hemodynamic effects of balloon pump, with the exception of pulsatility, have demonstrated effectiveness and are captured under the three categories of indications listed earlier to be proposed for reclassification into Class II.

In conclusion, while the literature may, at times, be equivocal, FDA contends that sufficient data has been provided to demonstrate sufficient evidence of safety and effectiveness of balloon pump for the indications encompassed by acute coronary syndrome, cardiac and non-cardiac surgery, and complications of heart failure.

There is currently insufficient evidence from the published literature that balloon pump for septic shock and IPFG are both safe and effective.

I will now turn it over to Karen for concluding remarks. Thank you.

MS. ULISNEY: Another table that may be difficult to read. Can

everyone see that okay? If not, again, I'll refer you to your slides and handout.

DR. YANCY: It's number 57.

MS. ULISNEY: Thank you.

So you've just heard the available scientific evidence related to the safety and effectiveness with regard to what is available in the literature for balloon pump devices.

With regard to risk to health, this table summarizes the risks identified by the original classification panel and other complications provided by manufacturers and discussed earlier in this presentation along with recommended mitigation measures for each risk. FDA believes that special controls can be established to mitigate the identified risks and provide reasonable assurance of the safety and effectiveness of balloon pump devices for the Class II indications we propose.

So, to conclude, our findings support the recommendation that there be no changes to the 1980 final rule for 870.3535, Part (a), Identification of the regulation or device description. We believe the device identification continues to represent the current technology.

However, the FDA is recommending the classification regulation be split based on the proposed indications for the use of balloon pump devices, to include both a Class II with special controls and Class III PMA classification. The Class II indications for use include ACS, cardiac and

non-cardiac surgery, and complications of heart failure. All other intended uses, such as septic shock and intraoperative pulsatile flow generation, require further proof of benefit and we recommend should remain in Class III requiring PMAs. Clinical data demonstrating sufficient evidence of safety will be needed to demonstrate the utility of balloon pump devices for these indications.

When evaluating the adequacy of the proposed special controls listed on this slide, it is important to understand that FDA correlates the ability of each special control identified here to mitigate an identified risk to health, discussed in this presentation.

The Class II special controls associated with this device are: validation of electromagnetic compatibility, or EMC, and electrical safety by appropriate analysis and non-clinical testing; appropriate software verification, validation, and hazard analysis must be performed; the device must be demonstrated to be biocompatible; sterility and shelf-life testing must demonstrate the sterility of patient contacting components and the shelf-life of these components; non-clinical performance testing of the device must provide a reasonable assurance of safety and effectiveness for mechanical integrity, durability, and reliability; and labeling must include a detailed summary of the device-related and procedure-related complications pertinent to the use of the device and appropriate warnings and contraindications.

Future device evaluation will not generally include clinical data. Through the 510(k) program, we are building on 30 years of knowledge and regulation of this device type. We have not generally reviewed clinical data for individual devices or indications in the 510(k) submissions. I think we talked a bit about that this morning. So there is no independent assessment or evaluation of the clinical performance, and as I mentioned earlier, indications for use have evolved over time in terms of what they mean and how the FDA has regulated them over time.

Therefore, we do not expect in the future that an independent dataset through clinical investigation will be part of our evaluation for specific indications.

Thank you very much. This concludes the FDA presentation regarding the recommendations for the regulation of balloon pump devices. And we look forward to your discussion and any questions.

DR. YANCY: Thank you very much. We are doing reasonably well on time. We have up to 15 minutes now to query the FDA in a brief fashion about specific areas where additional clarification is needed.

I'd like to take the prerogative, and just for the purposes of our discussion, Karen, you may want to defer to Marjorie, but could you just briefly summarize again the generic definition of a Class II device so we can have that exceedingly clear? We went over it earlier this morning, but I think we especially need to review it again this afternoon.

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And, Marjorie, if you'd like to come to the podium to do that, that'd be fine.

MS. ULISNEY: A Class II device is a device which cannot be classified as a Class I device because the general controls by themselves are insufficient to provide reasonable assurance of the safety and effectiveness of the device and for which there is sufficient information to establish special controls to provide assurance.

Examples of special controls are performance standards, postmarket surveillance, patient registries, and developing dissemination of guidelines.

Special controls may also include specific types of performance testing, such as biocompatibility, sterility, electromagnetic compatibility, pre-clinical testing or labeling, which FDA may outline in a regulation or a special controls guideline.

Most Class II devices require a clearance of a 510(k) prior to marketing. Sponsors are required to submit valid scientific evidence in their 510(k) demonstrating that the device is as safe and effective as a predicate device. Companies submitting 510(k) for a device must demonstrate how any specified special controls have been met in order to receive marketing clearance.

Examples of Class II devices include blood pressure cuffs, percutaneous catheters, electronic stethoscopes, and vascular graft

prosthesis.

DR. YANCY: Please do the same thing for Class III devices.

MS. ULISNEY: Certainly. A Class III device is a device which, one, cannot be classified as a Class I device because insufficient information exists to determine that the application of general controls are sufficient to provide reasonable assurance of the safety and effectiveness and the device; and, two, cannot be classified as a Class II device because insufficient information exists to determine that the controls would provide reasonable assurance its safety and effectiveness; and three, is purported or represented to be for use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health; or fourth, presents a potential or unreasonable risk of illness or injury. And they do require a premarket approval prior to marketing the device.

DR. YANCY: Thank you.

And, again, before we open up for additional questions from the Panel, let me remind you that in our earlier deliberations as we reviewed FDA questions, there was an opportunity to consider the classification of a device, recognizing that if it was deemed life-supporting and the classification was given for anything other than a III, there was a requirement to specifically support why that classification was given, but it does make it evident that a device can be classified as something other than

a III even if it is life-supporting.

So I wanted to get these definitions out front before we started our formal deliberations.

We heard quite a bit of information from the FDA. Thank you very much. It was really quite, quite clear and quite expansive. We heard a bit of information about the past history. We reviewed some of the most recent trials, many of which we keenly understand.

Part of the reason that Dr. Ohman is not with us this afternoon is that he's had a direct hand in acquiring much of this information and so has at least an intellectual conflict but did give me the benefit of his perspectives, which I can share with you later.

So, again, let's seek answers to questions that will provide more clarity, and we'd like to start with Dr. Allen.

DR. ALLEN: So I want to segue on what Dr. Yancy just spoke about because the conflict that I'm having the most trouble with is that I think most clinicians would consider this device life-supporting, which mandates a classification as a Class III unless we come up with mitigating circumstances to refute that.

I guess I'm looking for guidance from the FDA, because what I heard in the presentation was that the FDA perhaps no longer considers this device life-supporting, but it's used in conditions that are life-threatening? Did I interpret one of your slides that way?

DR. YANCY: If I can help you while they are putting their answer together, I think what the FDA is suggesting is that for regulatory purposes, this is thought to be appropriate to be reclassified as a Class II device, but it would require this additional language to indicate why it's a II instead of a III if we, in fact, decide that it's still life-supporting.

DR. ALLEN: No, I clearly understand that. I'm looking for -- because I'm trying to wrap my head around some rationale for that. And so I'm looking for guidance from the FDA as to why they think -- it sounds like, then, the FDA thinks it is a life-supporting device. I'm curious to get the FDA's input as to what they're considering a mitigating circumstance is. What's their reasoning?

DR. BROOKS: So this Steve Brooks from FDA. We agree that this is a life-sustaining device, but we feel that we understand the mechanism of action. We have 45 years of experience showing increasing safety with use of this device over that time period for a variety of indications. We feel that special controls can be written that Karen detailed that would describe the materials interactions in the human system, in the blood system, and we understand enough that we can write controls if we accept on a baseline level that there is effectiveness in these usages that we can regulate this as a Class II based on these controls.

DR. YANCY: So to be clear, your belief is that sufficient, unique controls, that it's not the general controls, but special controls --

DR. BROOKS: Correct, special controls.

DR. YANCY: -- to be written to qualify the use of the device.

Does that help, Dr. Allen?

DR. ALLEN: Yes, it does. I really just wanted guidance. I wanted to hear specifically their expression.

DR. YANCY: Dr. Kandzari?

DR. KANDZARI: Thanks. Great overview. And thank you for the information.

Karen, let me begin, just two questions for you. One is can you remind us -- you provided the Code of Federal Regulations device description and the general indications. But with regard to the product labeling, with regard to its utilization or its product labeling indication, is there anything specific about providing hemodynamic support versus reduction in myocardial infarction size versus improved survival? And, similarly, is there anything specific in the product labeling around site of vascular access, for example, axillary versus femoral, and also duration of support?

MS. ULISNEY: Very good questions. So with regard to your first question, the indications are very clinically oriented. It doesn't drill down any further to provide guidance in terms of the access site. Go ahead, Bram.

DR. ZUCKERMAN: No, no, no. Keep going. I'm sorry.

MS. ULISNEY: Does not provide specifics regarding that. When the 510(k) application comes in, specific indications will be listed for use, and those indications will be compared to the predicate device that comes in with the application. And, of course, they must match. But these are the series of indications that have been approved over many, many years, over almost four decades. And they have built upon themselves over the decades. Your final question --

DR. KANDZARI: Well, related to that also -- so very clinically oriented indications, as you mentioned, nothing about access site. Duration of support?

MS. ULISNEY: Duration of support is not a part of the labeling. What we did find in the clinical literature review was that their average time on support or duration of support was anywhere from 0, which would be attempting support to -- do you recall, Veronica? I think it was a hundred and so many minutes, or do you -- hours?

DR. BROOKS: So this is Steve Brooks. So --

MS. ULISNEY: Sorry.

DR. BROOKS: So the literature ranges from -- depending on indications -- so if it's used just for support during high-risk angioplasty, it may be an hour or less --

DR. KANDZARI: Yeah. Or today's, but --

DR. BROOKS: -- and it may go up to several weeks. The

indications on the label have not been so specific to indicate these granular points.

DR. KANDZARI: Got it. Thank you. And then the second question, Karen, is on slide 18, you shared with us the MDR reports, and the limitations of reporting notwithstanding. In 2009, there seemed to be a remarkable increase in frequency and device malfunctions that persisted for approximately a three-year period. Was there an iterative device change or was there a new product brought to the market at that time?

MS. ULISNEY: That's a really good question. And we actually looked at that further. So thank you for asking that. When I checked with our division that collects these MDRs, we were not able to really ascertain why the uptick in reporting other than, across the board, the division, the department received a larger increase of reporting for all devices. So it wasn't specific to the balloon pump devices. There was just an uptick overall of reporting in the MDR system.

DR. KANDZARI: There wasn't a "Dear Doctor" letter issued from FDA or anything, the Hawthorne effect in place or --

MS. ULISNEY: There was not. I did look into the recalls, and I think you have that in your Executive Summary as well, just in terms of, you know, the device safety and number of recalls, and they were extremely small. There were a total -- that would help -- there were a total of four recalls, Class II recalls, and two Class I recalls over a 10-year period. It's very

small.

DR. KANDZARI: Thank you. That's helpful. Thanks.

DR. YANCY: Dr. Naftel?

DR. NAFTEL: So I'm glad you asked Karen to read again the definitions of the classes. So I'm still -- I think I'm starting to understand, but let's just see if I do. So in Class II, you become Class II when you say the general controls aren't good enough to have a reasonable assurance of safety and effectiveness. And then it talks about Class II, if their performance standards and all, all things that sound like they're data patient-related. Then when we get into the controls, I know we'll do this in detail, but when we get into the controls, I look at all those, and it's like this morning; they're all non-human, non-patient stuff.

So it sounds to me like nothing pre, nothing out of the human body says anything about safety and effectiveness. So I think where we are is if you have these controls, you say I'm willing to infer that there will be safety and effectiveness in the human, but which is not in any way giving me any assurance. It's just saying I'm willing to infer that if I actually had data on the patients, it would be safe and effective. So am I confused?

DR. ZUCKERMAN: No, you're getting there, Dr. Naftel. And --

(Laughter.)

DR. NAFTEL: Getting to confusion --

DR. YANCY: Towards confusion or --

DR. ZUCKERMAN: You come back to some very good comments made by Dr. Brinker this morning and Dr. Allen's good question. So I do think we need to take a step back again and to explain to you how potentially life-supporting devices should -- could become Class II devices. It's not that they should. We're looking for independent advisory help here.

So, Karen, I'll take a crack at it, and then you can add. Let's take a step back and just realize that with certain classes of devices over time, we do get a wealth of evidence that can help us appreciate that as devices mature, there's a class effect for clinical benefit, and two, that the engineering matures towards certain standard designs. And this is what happens frequently in device iteration and maturation.

So to take an example that's independent of the one being discussed right now, let's talk about mechanical ventilators. Here's a good example where I think everyone would appreciate that these are life-supporting devices. But yet over a 30-year history by working with FDA, manufacturers have come to a point where we understand the design of these devices, we accept the fact that from a class/device perspective, we don't necessarily need data on each particular device, and these are Class II devices.

DR. NAFTTEL: So if I may -- so I think I'm really getting it -- so it's the words I'm strongly quibbling with. So the controls that are all pre-human controls, if you said those special controls along with the history of

clinical evidence leads to assurance, but the controls by themselves don't give assurance. It's what you said, the controls plus the clinical history?

DR. ZUCKERMAN: That's the general principle, but I'm just going to reverse it one way in that we need to hear from Panel members today whether that's the case with this particular class of devices.

DR. YANCY: But it does seem as if you're setting up a context here. You're saying that if we're thinking about a device that we know to be life-sustaining and life-supporting, if based on clinical experience we're comfortable enough with the technology, then we can rely on special controls for the Class II designation?

DR. ZUCKERMAN: Right. It's within our regulatory purview, but we really need your help to determine if that's the case.

DR. YANCY: Thank you.

MS. ULISNEY: And I think, you know, we also have to keep this in the context of this particular device is probably somewhat of an anomaly in terms of the life, you know, supporting factor in the 40 years of use and experience that we have with that both in the reported literature as well as the adverse event profile in the reported literature parallels very closely with what we've collected in our MDR adverse event database as well, which is what we consider fairly low.

Do you want to add some comments?

DR. YANCY: So why is it an anomaly?

MS. ULISNEY: Well, an anomaly in terms of this device has been on the market for 40 years. We have a lot of years of experience of collecting data at the FDA with MDR reporting, when MDR reporting began, and we know the adverse events that have occurred and that we have collected parallel very closely with the clinical research that has been presented. Does that make sense?

DR. BROOKS: So I can clarify that a little bit as well. So your question about the special controls seem to be all mechanical and bench. Special controls for a Class II regulation can be clinical data, a requirement for clinical data. With this mature technology, we believe that by having a balloon of a certain size that can inflate and deflate in the proper timing with the proper materials inside and the proper gases, we can get a class effect for the clinical effects that we're seeing for effectiveness and also for safety.

So we make the assumption that the clinical data body exists already, that we understand the clinical effect, and we can mitigate the safety risks by testing that can be done on the bench to determine that different devices that would be evaluated in this space perform appropriately, and we can describe/define the parameters that are important. In other such devices, if we could not, we may recommend as a special control clinical data. And that could be a performance goal based on a certain output or it could be a clinical trial. We have that ability.

What Karen is referring to is that over 45 years of usage, as the device has improved and materials and size and different indications, we understand the safety profile, we understand the materials, and we feel that mechanical -- the special controls that we've listed for you, we feel are adequate to understand this device and regulate it as a Class II.

DR. YANCY: Dr. Brooks, thank you.

Dr. Dehmer, please, and then Dr. Somberg.

DR. DEHMER: This is just a fairly granular question. It refers to your slide no. 59. On the classification, you list three classifications there. One is acute coronary syndromes. That one's easy. The next one, though, I have a question about. You have cardiac and non-cardiac surgery. In that broad category, do you mean to include using a balloon pump to support high-risk angioplasty, because technically, it's not really surgery, but is that included in that one?

MS. ULISNEY: I'll go back to the slide which might be helpful, which includes the cleared indications so you know what we have put in that bucket. Would that be helpful?

DR. DEHMER: I was referring just to slide 59.

MS. ULISNEY: Right. I understand.

DR. DEHMER: Does that include angioplasty, and if the answer's yes, then fine.

DR. ZUCKERMAN: It would be helpful, Karen.

MS. ULISNEY: So you said the cardiac and non-cardiac surgery?

DR. DEHMER: Right.

DR. YANCY: So that does appear in the ACS bucket.

MS. ULISNEY: In the ACS bucket.

DR. DEHMER: Okay.

DR. YANCY: Dr. Somberg?

DR. SOMBERG: I thought the FDA presentation was excellent.

Thank you very much on clarifications of many points here.

I have two questions. One is you discussed very briefly about how clinical practice has evolved, and it may be less beneficial now than I guess when I was a fellow and a young guy out there; it was the cat's meow, so to speak, and what we had to offer patients. Suffice it to say, the FDA doesn't regulate the practice of medicine, and I'm glad of that, but at the same time, they provide guidance. And if someone came to you with either a new device or the labeling of these devices in the new framework of Class II is some sort of -- would that be appropriate to discuss the evolution of the indications in where it might be best?

And that's not to say -- because current practice some places is to give thrombolytic therapy, and they may have a person that'll benefit tremendously from support. Other places may have done PTCA, may have done stenting, may have then taken them to surgery, and this person is

more -- shock, and there may be very little incremental benefit.

And I have another question when you finish on that one.

DR. YANCY: So what is the question just for clarity?

DR. SOMBERG: It's a discussion of labeling because we discuss that, yes, overall, this area is, you know, well developed, and it certainly sounds appropriate for down-classification. But a lot of the efficacy and safety data is 20, 30 years old. And it was pointed out, which is true, in the most recent studies, 2007, 2009, there is little, especially the SHOCK trial, et cetera, there's very little demonstration, if no, of efficacy. So is that going to be put into labeling, or are we just going to stay with the generic labeling as if it was 30 years ago where it made a tremendous difference.

DR. YANCY: So, Dr. Brooks, if you can give us some conversation about or discussion about the label as it currently exists?

DR. BROOKS: Okay. So I want to try and frame my comments here with my understanding of the first question here. So the FDA does not regulate medical practice. If I can put the -- we're going to use the same terms here, FDA, Class I, Class II, Class III, and then I'd like to refer to the ACC/AHA classification recommendations which use the same term, Class I, Class II, Class III; Class I being benefit far outweighs risks; Class II, benefit outweighs risk, there's IIa and IIb, IIb being benefit greater than or equal to risk; and Class III, no benefit or harm.

So how we have thought about balloon pump in the literature

to date, we believe that if you think of it in terms of the ACC/AHA Class III, is it harmful, if the answer to that is no, then you have agreed that this is either a Class I or a Class II ACC/AHA recommendations. And that point, you could -- the FDA would put it on the label as a labeled indication. The strength of the recommendation, be it ACC or AHA Class I, IIa, or IIb, we would leave to the physician expert groups, the literature, to further delineate what is the proper clinical usage scenario, what is the proper patient scenario, are there situations that it is best used.

But we believe that there is -- on the history, given the history of use, there is a hemodynamic effect, there is demonstrated use in situations in specific clinical scenarios, and by the three buckets that we've identified, we believe that there is enough to indicate the device and therefore recommend it in either a Class II FDA regulation or Class III regulation. But, however, we believe that it should be indicated for these.

DR. ZUCKERMAN: Okay.

DR. YANCY: We need to do this --

DR. ZUCKERMAN: Dr. Somberg, could I just interrupt a moment -- I'm sorry, Dr. Yancy -- did Dr. Brooks answer your question about labeling? It's an important one.

DR. SOMBERG: Well, he presented an answer. It was a very formalistic answer. I would be more --

DR. ZUCKERMAN: Okay. Here's a --

DR. SOMBERG: Let me just say I would --

DR. ZUCKERMAN: Okay.

DR. SOMBERG: -- be more suggestive that one give thought -- and I'm not saying I have the answer -- but one gives thought to pointing out -- because many times labels, whether it be drug or device, has some guidance there -- it's not the regulation, but it's a guidance -- and that your point was well taken in your presentation that over the course of 45 years, as you said, the benefits have evolved. And take note, cardiologists or cardiac surgeon, in the placement of it, there may be areas of greater or lesser utility. That's all I was saying. I'm not against your presentation or proposals here.

DR. BROOKS: Right.

DR. SOMBERG: I think they're very well taken. But I'm just saying that guidance is very important.

DR. BROOKS: There has been some sprawl in the indications that have gotten onto the labels, and today and tomorrow are about trying to think about these rationally as we go forward, as devices evolve or as regulation evolves, and put them into categories that we can manage, going forward.

DR. ZUCKERMAN: Okay. To just keep it simple, Dr. Somberg, and other members of the Panel, we do want to get your input on how the label for this class of devices could be revised to be consistent with the data

and good clinical practice in the year 2012. And I'm sure when we get to that question, you'll be able to help us.

DR. YANCY: Thank you, Dr. Zuckerman. I think there was one more question from the Panel, and that'll be from Dr. Cigarroa.

DR. CIGARROA: Just a point of clarification with regards to ACC/AHA guidelines. One can be a Class III guideline, not harm but no benefit, so just because there's not harm does not shift one from a Class III to Class II. It's either harm or no benefit.

DR. YANCY: Thank you for that clarification. Now, what I'd like --

DR. SOMBERG: I had the second part of my question.

DR. YANCY: We really need to move forward with our Open -- our Public Hearing. We will have an opportunity to come back to this series of questions. So if you can hold that question, Dr. Somberg, at the 4:00 hour, we can begin with that, so if you'll indulge me, I'd appreciate it.

I want to thank the FDA for presenting us a very clear set of data points and providing very thoughtful answers.

At this point in time, we need to proceed with the Open Public Hearing. This portion of the meeting is to give the public an opportunity to comment on the issues that we are deliberating. Public attendees are given an opportunity to address the Panel to present data, information, or views relative to the meeting agenda.

Ms. Waterhouse, our Designated Federal Officer, will now read the Open Public Hearing disclosure process statement.

Ms. Waterhouse?

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 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 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. YANCY: Thank you, Ms. Waterhouse.

We have record of three parties who have requested to speak during this Open Public Hearing, and we have approximately 20 minutes to complete this hearing, so I'll request that each speaker respect the time

limitation quite closely.

Let me be certain that the speakers are in the audience. Someone representing the National Research Center for Women and Families? Thank you for being here yet again.

Dr. Alan Gass, Medical Director of Cardiac Transplantation and Mechanical Circulatory Support, Westchester Medical Center, New York Medical College? Thank you for being here. Not yet.

And then Atman Shah? I do know that Dr. Shah is here. I saw him earlier. Yes.

So we'll begin with our representative from the National Research Center for Women and Families. And please restate your name.

MS. FRANCE DE BRAVO: Good afternoon. As I was earlier, I'm still Brandel France de Bravo, and I'm pleased to have the opportunity to speak a second time today on behalf of the National Research Center for Women and Families. Our center does not accept funding from device companies, and I have no conflicts of interest.

Our nonprofit center analyzes and reviews research on medical issues and provides objective and understandable information to patients and providers. And as I stated earlier, we're an active member of the Alliance for a Stronger FDA, a nonprofit coalition of corporations and nonprofit organizations that has successfully increased resources for the FDA by billions of dollars.

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We strongly agree with the FDA that IABP devices used to treat septic shock and intraoperative pulsatile flow generation should remain Class III, with PMAs required. I guess that's not surprising. The evidence of safety and effectiveness for these indications has yet to be established.

The much more difficult question Panel members must answer today is whether the evidence base is sufficient to down-classify IABPs to Class II with special controls for acute coronary syndrome, cardiac and non-cardiac surgery, and complications of heart failure, both ischemic and non-ischemic, which is, of course, what the FDA is recommending.

Now, the safety record for 75,000 IABPs used per year in the U.S. is respectable given that the FDA notes that the intended population is a group of patients with very high morbidity. And we agree with the FDA when they say that the number of reported deaths which were 189 during the last 10 years is not necessarily reflective of the device itself but the very sick population in whom it is used. Of course, there may be many deaths that were not reported. That is a problem with the reporting system.

An important question is how effective IABPs are for the uses specified under their proposed down-classification. According to the Code of Federal Regulations, "there is reasonable assurance that a device is effective when it can be determined, based upon scientific evidence, that in a significant portion of the target population, the use of the device for its

intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results."

Now, PowerPoints are, by necessity, very reductive, so let me turn your attention just for a moment to the FDA's more in-depth Executive Summary, where words like "no benefit," "conflicting," "confounding," "equivocal," "may improve," "may have a beneficial effect," appear over and over in the sections pertaining to proposed Class II indications. For instance, a concluding paragraph on page 24 says, "While the literature may at times be equivocal, FDA contends that sufficient data has been provided..."

This sounds more like wishful thinking than science. We therefore disagree with the FDA's recommendation to down-classify, given that this is a life-supporting device.

Now, after a semi-implanted device has been in use for over 40 years, or 45 years, as people have specified, it's pretty hard to admit that we don't know as much about its effectiveness as we would like. Isn't it time to change that?

About IABPs for acute coronary syndrome, which is a Class II indication as proposed by the FDA, the FDA writes in its synthesis: "Trials performed to investigate the benefits of IABPs using the modern standard of care have been underpowered to demonstrate improvement or have had other limitations such as variability in the timing of IABP usage." And we

saw that on the slides.

Now, the reference to timing is an attempt, of course, to explain the results from the IABP-SHOCK II trial, which, pardon the pun, were shocking to me just because this obviously is not my area of expertise, so I was shocked to find no difference in mortality between the IABP and the control group. But then apparently, in the U.S., IABPs are placed earlier than in Germany, where the trial was conducted, and this, to use FDA's language, "may" affect effectiveness.

FDA decisions are supposed to be based on science, and your recommendations to the FDA should be based on scientific evidence. We're not helping patients if we approve devices based on assumptions rather than science.

Now, as I mentioned this morning, the court decision this week would allow companies to promote their medical products for off-label uses. Therefore, we should not be splitting these classifications unless there's a very, very strong rationale to do so.

In this case, there is insufficient evidence that the device works for all of the so-called Class II indications. And even if the controls stipulated a postmarket study somehow distinct from surveillance, it could take more than a decade before we have clinically useful information. Meanwhile, a product that could be ineffective for the indications for which it was cleared would be used by thousands of patients. And I just want to

remind everybody that when a product doesn't deliver very clear benefit, no level of harm or risk is acceptable.

DR. YANCY: We'll need you to sum up, please.

MS. FRANCE DE BRAVO: Yeah, last sentence. In conclusion, IABPs should have been studied in clinical trials decades ago. The companies have had an almost free ride, and it's time that the FDA demand research evidence. Thank you.

Brandel France de Bravo. Thanks.

DR. YANCY: Thank you, Ms. France de Bravo. I have your name in front of me now, so I won't have a difficult time anymore.

Dr. Alan Gass, please? Please restate your affiliation and whether or not you received any support.

DR. GASS: Sure. Good afternoon. My name is Dr. Alan Gass. I'm the Medical Director of the Transplant and Device Program, Westchester Medical Center. I have received compensation to come to this meeting.

My present position over the last -- present position and previous position, I have 22 years of experience in device technology, and I've seen the evolution from the infancy of balloon pumping to three generations of ventricular assist devices and also the total artificial heart.

We've now come full circle so that we're now entering into an era of non-surgical percutaneous devices for mechanical support, devices like the Impella, the Tandem and percutaneous ECMO. Throughout this

evolution of technology, the balloon pump has remained the safe and important therapeutic option for the indications that were discussed, acute coronary syndromes, mechanical complications of myocardial infarction, specifically acute mitral regurgitation, acute decompensated heart failure, preop stabilization, bridge to transplant, bridge to implantable device, and more recently, use in conjunction with peripheral ECMO. In addition, over the years, this device has had many modifications to improve safety and efficacy.

My personal experience has been mostly in the use for acute decompensated heart failure as a bridge to transplant, as a bridge to an implantable device, and more recently using it in conjunction with 200 peripheral ECMO devices. So, clearly, these patients are the sickest of the sick.

Looking at our experience this year in 2012, we've put in over 150 balloon pumps for the various indications. And sitting on the Quality Committee of Cardiac Surgery, Surgery and Cardiology, we've had one major complication.

My review of the literature, as mentioned here, I think one interesting thing is that if you look at the SHOCK II trial, as far as safety, in the predetermined secondary endpoints that you would predict would be higher in the balloon pump arm, meaning stroke, bleeding, peripheral vascular complications or sepsis, there was no statistical increase for the

balloon pump arm. I do agree that there was no significant impact on mortality, but as also mentioned here, there were many variables, as far as time of implant, degree of revascularization, preexisting myocardial dysfunction.

I think what's interesting, if you read the article, the patients that were supported with balloon pumps may have had more aggressive revascularization, and I think that may translate into improved 6-month and even 1-year survival benefit.

So, in conclusion, I think that this is a safe and effective technology, and I think as mentioned recently, it has survived peer review, and it remains a Class Ia indication for the clinical scenarios that we have discussed today. Thank you very much.

DR. YANCY: Thank you very much, and thank you especially for respecting the time limitations.

Dr. Shah, please? State your organization and whether you received any support.

DR. SHAH: Thank you, Dr. Yancy and members of the FDA Panel. My name is Atman Shah. I'm an interventional cardiologist and Co-Director of the Cardiac Cath Lab at the University of Chicago. I have several conflicts I wish to disclose. I serve as a consultant for MAQUET and has received travel expenses and reimbursement. I have also served as a consultant for Abiomed and Medtronic and have received research support

from the NHLBI R01 HL076671 for research in cardiogenic shock.

DR. YANCY: Please pause for just one moment.

DR. SHAH: Thanks.

DR. YANCY: Thanks.

DR. SHAH: Thank you.

I think as a clinician and as all the clinicians here in the audience, I think there's a certain number of patients who we've seen will benefit from intra-aortic balloon pump treatment. In the last two weeks, I just want to relate three stories of patients who have benefited and I think would -- these are the type of patients who would benefit in the future.

The first was a 75-year-old grandmother who had an acute anterior myocardial infarction, came in through a pre-hospital 12-lead ECG system, and she was -- had a heart rate of 114; her blood pressure was 90/60; the paramedics had started her on dobutamine and dopamine, and she had rales halfway up her lung. Prior to opening up her LAD after doing thrombectomy, we placed a balloon pump, and she did quite well. She had enhanced diuresis and she had a three-day hospital visit. Afterwards, she's completing cardiac rehab.

But I think the spectrum of patients who can benefit from intra-aortic balloon pump counter-pulsation expands beyond the acute anterior STEMI population. We had a 20-year-old college student from Southern Illinois who came in with acute viral myocarditis and an ejection

fraction of 10% whom we bridged with a balloon pump, as Dr. Gass mentioned, commonly, to LVAD and then eventually to transplant.

And I think a unique population, which was touched on earlier by Dr. Brooks was while most of the benefit -- the greatest benefit seen with IABP early on was in patients who received fibrinolytics. We had a patient from another hospital who was treated with fibrinolytics and was still in shock and then had a balloon pump placed for transport and then came to our institution.

So I think the broad spectrum of patients in acute coronary syndrome assistance with high-risk PCI and in heart failure, the balloon pump has continued value.

If there's a couple of points I may make about the CRISP AMI trial, the ISAR-SHOCK trial, which I think have been excellently summarized in the past couple of minutes, the CRISP AMI trial, again, there was the -- one of the really neat things was that the door to balloon time was not impacted by the implantation of the balloon pump. The door to balloon time was still about 77 minutes compared to 68 minutes in the PCI-only arm.

But what was remarkable is that while it didn't hit its primary endpoint, which is a reduction of infarct size by MRI, there was almost a doubling of patients in the PCI-only arm that had TIMI 3 flow at the initial angiogram compared -- there was about 12% of patients who had TIMI 3 flow in the PCI-only arm compared to 6% in the balloon pump-only arm.

Could that have changed the final endpoint? Possibly. The p-value was 0.06, and a near doubling of better flow could have impacted it.

And I think the really important thing for the CRISP AMI trial was that there wasn't an increase in peripheral complications. There wasn't increase in stroke; there wasn't an increase in need to go to peripheral bypass surgery.

And then commenting on the ISAR-SHOCK trial, I think both of these were wonderful trials. I think, getting to the previous speaker's point, having a very large trial is very difficult to do, and oftentimes, we're left with imperfect data and we're forced to make perfect conclusions. With the ISAR-SHOCK trial, it was a composite of not only non-STEMIs and STEMIs -- and another red herring was that the timing of the pump was left to the discretion of the interventional or the revascularization specialist, with the majority of them being placed after revascularization.

Now, mortality was not different in those who got balloon pump prior to revascularization to those who got it after revascularization. But if more patients had received balloon pump therapy who were in cardiogenic shock prior to revascularization, could this have improved the hemodynamics of the ventricle? We do know that in animal studies, that implementation of an intra-aortic balloon pump can decrease the harm from the ischemia reperfusion syndrome in an occluded artery.

So with that, I'd like to thank you for your time and patience.

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Thank you.

DR. YANCY: Thank you very much, Dr. Shah.

At this point, I'd like to open the podium to any parties in the audience who might wish to speak during this Open Public Hearing.

(No response.)

DR. YANCY: None have come forward.

As a Panel, we can now take the next several minutes to direct specific questions to either Ms. France de Bravo, Drs. Gass or Dr. Shah regarding any of the subject matter presented by those three individuals.

I'll share with you that Dr. Ohman was one of the lead investigators in the CRISP AMI study, and the notes that he shared with me before he left were to emphasize that even though the endpoints were not statistically significant, his view was that the device was, in fact, quite important in stabilizing hemodynamics and that a big question in terms of the interpretation of the results has to do with a delta of time for PCI that was required for placement of the intra-aortic balloon pump.

But he felt that as an investigator, there was still evidence that those that had compelling hemodynamics were benefited by the balloon pump. And a post hoc, small subgroup analysis that was not prespecified did suggest that the persistence of cardiogenic shock was less in the groups supported with the balloon pump a priori than those without.

Are there additional questions or concerns regarding any of

the information we've just heard?

(No response.)

DR. YANCY: Hearing none, then, I will declare this Open Public Hearing Session as being closed. This will give us an opportunity to capture a bit more time which I think will be required for our deliberations.

At this point in time, I think we should go ahead and proceed with our scheduled break and reconvene in the next 15 minutes. We'll begin with Dr. Somberg and allow him to pose his question to the FDA, and I appreciate your tolerance. So thank you for waiting.

(Off the record at 3:27 p.m.)

(On the record at 3:44 p.m.)

DR. YANCY: Let me have your attention. We will now resume our meeting. This is the time that is set aside for our Panel deliberations. We have an additional 15 minutes over the allotted time thanks to our efficiencies during the day, which is probably time that we will need.

As promised, we will begin with Dr. Somberg, who now has several important questions that need to be addressed by the FDA. One is about the 510(k) process. Any others Dr. Somberg will articulate for us.

Is the FDA ready for their responses to Dr. Somberg?

DR. SOMBERG: Just ask me if I'd ask the question again --

DR. YANCY: But I just want to get them to the table --

DR. SOMBERG: But I can -- okay.

DR. YANCY: Yeah, please go ahead.

DR. SOMBERG: This is John Somberg, and I just wanted to say that I don't want this to be misconstrued in that I do support the down-classification based on the very excellent presentation for the intra-aortic balloon.

With that said, with any process, regulatory, legislative, there's always a pendulum goes to the extremes. And I just had a concern in my mind is, yes, we're talking about down-classification here from a Class III, and this is a life-sustaining/supporting device, but I do believe we have enough information now to have special controls to guide in the 510(k) process for future devices.

But I conceive very clearly, although I can't do it myself in my mind, that there's going to be miniaturization of these devices, and you're going to see a device in the coming years that can be possibly implanted or it would be inserted and have a very minimal tethering to an external gas or something of that nature.

How would you deal with that in this process? Are we setting up a conundrum whereby we put ourselves in a straightjacket and we would have to accept that as a predicate for these new type of devices, or does the regulatory area have enough of leeway to be able to say, well, they're not substantially equivalent and we would need this to be a PMA because of such a change in the risk/benefit ratio?

MR. AGUEL: Okay. So I will clarify that what we will look at today and my answer will be --

UNIDENTIFIED SPEAKER: (Off microphone.) Can you say your name?

DR. YANCY: Will you speak closer to the microphone as well?

MR. AGUEL: Sorry. Fernando Aguel, Acting Senior Reviewer and Team Leader for Circulatory Support Devices Branch in the Division of Cardiovascular Devices.

So I'll predicate my answer on that going forward from something that may be established as a Class II device with special controls regulated through the 510(k) process. So we currently already do have a mechanism for looking at technological advances, next devices and next device iterations for devices that are Class II. And presuming that a manufacturer would come up with an advancement and submit that as a 510(k), in our review process, the first thing we do is ask whether or not the device has the same intended use. So in the case of miniaturization or something that becomes an implant, the answer to that may change, may not be yes.

If it does, however, have the same intended use, the next question that we ask is whether or not there are technological changes to the device. And that can include making pieces smaller, including different materials, for example, or using a different gas to drive the system, in this

case, and if there is that change, then we ask ourselves the question of whether or not this can affect the safety and effectiveness of the device.

If the answer to that is yes, then we have the recourse to go put that device into Class III and require a PMA. If the answer to that is no, then we can continue using the already cleared device as a predicate device to establish substantial equivalence.

DR. YANCY: So if I understand this exchange, the question was specifically if a device that is in principle a balloon pump comes along but that is substantially different from an engineering standpoint, you have a process in hand to determine if it can be approved based on the predicate devices or if it's sufficiently different as a reengineer platform that it needs to undergo independent review.

MR. AGUEL: That's correct.

DR. YANCY: Is that satisfactory, Dr. Somberg? And you had a second issue you wanted to pursue with the FDA; is that correct? That's the only question?

I would like to thank the FDA for coming to the table. While you're there, before you depart, based on the earlier information, here is another opportunity to query the FDA before we start our internal deliberations.

So we have several questions. Dr. Greenfield, then Dr. Doty?

DR. GREENFIELD: Thank you. My question has to do with

experience in the pediatric population, where balloon size would be a little more critical and whether or not this was a factor in any unique or more frequent MDRs?

DR. BROOKS: I'm not aware of any outsized representation of the pediatric population in the MDRs. We didn't have a lot of the granularity, and when you read through the summary reports, and we did that for all of the mortality data from the last three years and a sampling of the other, there is often not details about the patient age. So the reporting is very valuable. So the answer to your question is we're not aware of misrepresentation or an outsized number of safety issues in the pediatric population.

DR. GREENFIELD: Do you have data on utilization in the pediatric population?

DR. BROOKS: We do not have any IDE studies, we don't have any clinical data that's been presented to us, and I'm not aware of any companies that have sought a specific indication in pediatric use.

DR. YANCY: Dr. Doty?

DR. DOTY: Dr. Brooks, do you think you could comment on the use of the balloon pump in non-cardiac surgery? I think this is an extremely unusual indication for it. Maybe the data I'm aware of is really just isolated case reports. And so could you comment on the FDA's recommendation to move to Class II for that specific --

DR. BROOKS: Yeah, so I agree with your assessment of the literature. There really are not any good randomized studies. In the 2009 ACC/AHA guidelines and recommendations, they summarized it just as you did; there are no good randomized studies, and we cannot evaluate it even to give it -- the level of evidence -- we cannot give it a Class I, Class IIa, IIb, or III recommendation because there isn't enough.

However, that being said, we agree that the mechanism of action is the same regardless of whether it is a cardiac surgery or non-cardiac surgery indication. And by extrapolating from the cardiac surgery literature, we feel that the safety is the same, it is a very safe device, and we can put adequate assurances around the use in that situation.

We would look to your advice as the Panel for commentary on that, and that's one area that the evidence is sparse, and we would look for some guidance.

DR. YANCY: Dr. Lange, if you can speak to this question, that would help.

DR. LANGE: Go back to slide 13 for a second and just -- I think it's just a misplaced bullet point, or so I understand, but if not, I'm having a hard time understanding what this means. And it's the second point under cardiac and non-cardiac surgery. Just for clarification. Slide 13. Thank you, Jamie.

The second point, should that be two separate thoughts?

Instead of cardiac support for non-cardiac surgery, prophylactic support in preparation for cardiac surgery? If not, if someone could explain what that is?

DR. BROOKS: That is how it read in one device label, apparently.

DR. LANGE: Okay. Well, perhaps we want to think about --

DR. ZUCKERMAN: Okay. So Dr. Lange, that's an excellent point. Would you be more happy with just cardiac support for non-cardiac surgery?

DR. LANGE: Yeah, otherwise I don't understand what it means. Thanks.

DR. YANCY: I guess the question becomes what are those cases?

DR. LANGE: Yeah, in other words, what are those cases, and the second is if these are cleared indications by categories -- so I guess I'm a little confused because on the one hand you're saying this came from somebody else's product, but are these the cleared indications from the FDA or not?

MR. AGUEL: Yes, they are, and I do want to clarify one point. Those are two separate indications, so they were meant to be separated, and it's just a bullet point issue.

DR. LANGE: Thanks. That helps. And then, so what is cardiac

support for non-cardiac surgery? I mean, what -- either for the surgeons or for -- let's clarify what that is.

DR. BROOKS: So in the studies, it would be balloon pump use for patients who had high cardiac risks that were undergoing another procedure, could it be a GI procedure, endoscopy, something else that is not a non-cardiac surgery, but these are high-risk cardiac patients.

COURT REPORTER: I'm sorry. Before you guys from the FDA speak, would you please state your name for me?

DR. BROOKS: Sorry, that's Steven Brooks.

DR. YANCY: So are any of my surgical colleagues on the Panel aware of cases consistent with this cleared indication?

Dr. Doty, Dr. Yuh, Dr. Katz, Dr. Allen?

DR. ALLEN: So I can comment on that. I've never seen one, but I know of the literature. There are case reports of two or three patients having major abdominal surgery or lung resection where, again, they have high-risk cardiac disease that either wasn't amenable or, at the time, years ago, wasn't, you know, revascularized prior. So it was a support mechanism through the operation recovery period. But, again, it's scattered case reports.

DR. YANCY: Any other input? Dr. Yuh?

DR. YUH: My experience with the literature is the same. The difference, I think, between this situation and support for cardiac surgery,

though, is that in cardiac surgery, you're -- or even for acute coronary syndrome, you're actually addressing the problem, you know, whether it's revascularization or whatnot. With this balloon support, in most of the cases that I'm familiar with with respect to non-cardiac surgery, you're really not addressing the cardiac problem. You're temporizing things with the balloon during that stressful perioperative period, but afterwards, you're withdrawing that without having addressed the cardiac deficiency.

DR. YANCY: Dr. Katz and then Dr. Allen?

DR. KATZ: Yeah, I think it is very important that those two issues are separated because prophylactic support in preparation for cardiac surgery is an accepted, well-documented utilization, whereas I think as we're hearing here, there may be scattered episodes of use of a balloon pump for non-cardiac surgical procedures, but it certainly doesn't fit in with the other well-documented utilizations.

DR. YANCY: And Dr. Allen?

DR. ALLEN: Yeah, we had a case several years ago in which a patient was diagnosed with a critical left main and was going to have surgery but developed a perforated viscus shortly after being cathed, and actually had a balloon pump placed, and then went to surgery, or went to have their viscus repaired through an abdominal operation. So I think most of the cases for non-cardiac would be emergent setting. It's hard to get my head around why you would do that on an elective basis, as David then says, but

when you're not really addressing the cardiac problem.

DR. YANCY: Dr. Kandzari?

DR. KANDZARI: Two comments. Just to share with you, I had a patient on Friday, for example, who has an ejection fraction of 15%, is on inotropic support, who developed small bowel obstruction, and his systolic blood pressure is 75, and we were asked to put a balloon pump in to support him through surgery. So these instances are out there.

I want to just, while we have FDA here, to clarify two issues with you that would help provide us guidance in our deliberations. Uniquely in the device history, at least for me, this is one device whose product labeling offers very little opportunity for off-label use because it's so broad, right? And as Steve described, this is a good opportunity for us to clean that up.

And to that purpose, two questions I have for you, is it uniquely in device history, too -- for me, we have balloons that are designed to improve luminal diameter, stents that improve luminal diameter; there is some mechanistic purpose within the product labeling. Here there are clinical indications, Karen, as you so well described. But it seems to me like it would be purposeful for us to consider the product labeling to improve hemodynamic support or to improve hemodynamics. You can argue about improved coronary blood flow, et cetera, but the device, rather than just saying this is a device that inflates and deflates and its indications are X, Y

and Z, it seems like we should include some language around what the intended purpose is, and that is hemodynamic support.

And I'd like your comments on that. And, secondly, we also oftentimes consider in product -- in the actual IFU the inclusion of clinical trial data. And there has been, as Steve so well described, numerous studies recently, very recently describing the absence of benefit and not only cardiogenic shock, but in high-risk prophylactic use and high-risk PCI, the BCIS trial being one of those examples.

And if we were to consider the inclusion of those data to be referenced in IAB product labeling, given that those trials are exclusively non -- with the exception of CRISP AMI, many of these studies are non-U.S.-based studies -- do you have any challenges with the inclusion of that? And this is David Kandzari, for the record.

MR. AGUEL: So to answer your first question, with the possible addition of mechanistic purpose in the labeling for the -- sorry, this is Fernando Aguel. To answer that first question, with regards to adding the mechanistic purpose to the device, I think that's something that is a possibility. And we look forward to your suggestions on that, your advice on that and what to include in the labeling, if that's a decision we go to, to include labeling as special controls and develop them, is what types of information should be included in the labeling.

DR. YANCY: So that's a very good suggestion. I really want to

thank the FDA again for being so accessible and providing such thoughtful responses to our queries.

It is approximately 4:00, and we have --

DR. KANDZARI: You were going to comment on non-U.S. data?

MR. AGUEL: And so to comment on that real quick, if I may,

Dr. Yancy,

DR. YANCY: (Makes a sound.)

(Laughter.)

MR. AGUEL: That I do not believe that there's an issue with including that data. That's available in the public domain and in literature and labeling. But, again, we'd be looking for your advice into what sorts of information should be included in the labeling.

DR. YANCY: Is that satisfactory, Dr. Kandzari?

DR. KANDZARI: Yeah. Thank you. Pardon us.

DR. YANCY: Okay. Terrific. It's time for us to move forward with our Panel Deliberations. We have approximately an hour dedicated to discuss a very important question here, recognizing that some of this may be precedent-setting or at least a template for future deliberations as early as tomorrow.

The purpose of this portion of the schedule for Panel Deliberations is to allow time for us to address our questions amongst ourselves in detail. Once we have begun this deliberation, in general, it is

amongst Panel members, and we won't reengage FDA unless there is a very specific inquiry. We will at the end of this time period then have FDA, Karen, present the questions to which we will formulate specific answers.

So with that in mind, Karen, can you put slide 60 back up? That is to provide -- thank you -- that provides the substance for which we have to discuss. Ultimately, this is where we need to be, making a decision yet again about reclassifying a previously approved Class III under the 510(k) schema now as a Class II with special controls.

Questions have already been raised about what those special controls would necessarily entail, whether the device is indicated for acute coronary syndromes, and we saw there are several specific things that qualify for acute coronary syndromes, including high-risk percutaneous interventions, cardiac and non non-cardiac surgery -- we've heard at least the anecdotes or the case involved there -- and complications of heart failure, ischemic or non-ischemic etiologies, including bridge to transplant and bridge to left ventricular assist systems.

For that entire suite of indications, the proposal is to move to Class II. For the others, specifically, septic shock and intraoperative pulsatile flow generation, the recommendation from the FDA is that it remains a Class III designation, as was the case when the devices were first approved, and in order for this indication to go forward, it would require premarket approval either with already existent data or the acquisition of de novo information.

So with that in mind and understanding what kinds of questions we will need to answer, based on our earlier deliberations, why don't we begin our discussions, and it seems reasonable to start with that which is most compelling, that is, reclassifying this from a Class III to a Class II for the stated indications.

Dr. Cigarroa, please begin.

DR. CIGARROA: So I'll focus initially on the issue of reclassification from Class III to Class II for acute coronary syndromes. Our bias often is that doing more, i.e., PCI or mechanical approaches to solving issues with regards to acute cardiology presentations may, in fact, improve outcome. With regards to IABP, the most recent datasets, specifically the reference to high-risk PCI and the management of cardiogenic shock in the setting of acute revascularization, has been disappointing.

When one takes a look at the German study on the SHOCK IABP trial, mortality rate in both arms, 40%, no improvement in TIMI flow post-procedure, and no difference in amount of inotropic support through medications either in magnitude or duration.

That said, I think the clinical judgment here about clinicians being able to employ this device in a group of patients with an incredibly high morbidity and mortality is such that I would favor reclassification despite the paucity of the data.

DR. YANCY: Certainly, I think the editorialists that provided an

opinion along with the publication of the SHOCK II results were quite clear, indicating that what the data really tell us is that something else needs to be identified for this group of patients with a 40% risk of death. And I think that was well stated.

Dr. Dehmer?

DR. DEHMER: Well, I too would agree to support reclassifying it for these indications to a Class II. I agree with what Dr. Cigarroa has said about the results being somewhat disappointing. And although at least in the SHOCK II trial, the German study, there was no difference in 30-day mortality, I think those who have, as I'm sure many of the individuals on the Panel who have cared for patients like this, have come to realize that there are oftentimes where the intra-aortic balloon pump can provide that one hour, two hours of stabilization or that little bump to get people over the hump. And yes, some people make it; unfortunately, a lot of people don't. But I would certainly, based on a lot of clinical experience, would support this being a Class II.

DR. YANCY: And arguably some of the disappointment in the SHOCK II results could be because of sample size and approach and trying to understand what the real magnitude or benefit is, thus, what the real power would need to be --

DR. DEHMER: And I would add that the SHOCK II trial were all patients that were committed to a revascularization strategy, which, by

virtue of the fact that they all got revascularization, were a different group from what we saw the benefit in the past where they were not revascularized. It may be harder to show a benefit. And those that undergo revascularization and do poorly are, in fact, an extremely high-risk group.

DR. YANCY: Thank you, Dr. Dehmer.

I really don't want to rush through this piece because this is a critical part of our deliberations today, to accept the recommendation to reclassify intra-aortic balloon counter-pulsation from a III to II, particularly for this acute coronary syndrome space, which again includes a number of different iterations that are defined by cleared statements from the FDA as acute coronary syndrome, so I'd like to get more feedback from everyone around the table even if it agrees in principle with what's already been said.

Can I call on you, John?

DR. HIRSHFELD: Sure. I'll be happy to agree. And I say this from a perspective of having heard Adrian Kantrowitz give medical grand rounds at the New York Hospital in 1968 when he first described his first experience with this, having put in the surgically implantable 15 French devices that first were commercially available and now putting in 7 French devices.

So I think this is a very valuable technology which is really integral to taking care of critically ill patients. It's a paradigm of the benefits of create a sophisticated engineering refinement over a long period of time,

so we now have devices that work very well and are very safe certainly compared to what we had to work with in the past.

I'm not concerned about the poor outcomes in the population studies because I think that anybody who has a significant experience with these devices knows that within the population, there are people, individuals, who have dramatically benefited by the device, and other individuals in whom the device is either ineffective or is not adequate to salvage them.

And so I think to hide behind the population data and therefore decide that the device is of no value is really having excessive blinders on.

So I think this is an important group of devices that deserve to be in Class II.

DR. YANCY: Dr. Hirshfeld, thank you very much.

Dr. Katz, if you can give us the surgical perspective, that'd be great.

DR. KATZ: Sure.

I basically agree with what's been said. I think one of the keys about balloon pumps is that they really were and in many ways still are the first toe in the water, so to speak, of assist devices. And as the patient populations have gotten more acute and sicker, and there are more devices available that's being compared to a whole different population of patients

than were really ever intended to use in, and being compared to devices that are new generations beyond it.

But for its appropriate utilization, it's worked remarkably well for a remarkably long time with really only iterations to it. So I would fully support these changes.

DR. YANCY: Thank you, Dr. Katz.

Dr. Brinker?

DR. BRINKER: I didn't want John to establish himself as the eldest person here without -- I was in medical school when Kantrowitz, who is a professor at my university, presented that data as well. And he made the important observation that if you don't do anything for these patients, they're going to die. And I think we have to realize that. In most of the patients we see, this isn't a curative, therapeutic procedure. This is a supportive procedure. It doesn't cure anybody of anything. And without the appropriate follow-up, patients aren't going to do well. It buys time, I think, and it does that well.

And as far as efficacy goes, there are enumerable studies that show an increase in mean aortic pressure, and increase in cardiac output, a decrease in preload. And in patients with significant coronary narrowings, an increase in coronary blood flow to the ischemic area. So if we use that as a measurement of efficacy -- and of course we'd all like to see survival, but I don't think that the survival, at the end of a period of time, is a function of

just the balloon; it's the function of what comes after it.

DR. YANCY: What is interesting about all of the comments so far is that they're from the context of a wealth, and I do mean to say wealth, of clinical experience, and I highlight that only because I think that it informs the deliberations that need to happen on tomorrow, in terms of understanding where you position devices. So I just want to bring that to the table for the purposes of the Panel discussions.

I do think it's still important that we capture other thoughts on this one issue.

Dr. Allen, then Dr. Yuh?

DR. ALLEN: Well, I'll start off by saying that I do agree by saying that I do agree with the reclassification, but I think I need to be intellectually honest that when you look at the discussion that we're having now, and you kind of take a 30,000-foot look at it, and you're looking down and listening, we're defending clinical biases in the face of recently published negative clinical trials. And that hits us over the head. And our first reaction is those trials can't be true. And historically -- I've heard this from distinguished researchers, that sometimes our clinical biases, no matter how ingrained they are, are often clearly wrong.

DR. YANCY: Point well made. And there are any number of examples where things that we thought were just definitive, once studied in a more deliberate way, we change our opinions. One might look differently

at this discussion and say that what we're deliberating is the question of absolutism, that is, a yes or a no, should the devices continue as they have been, whereas the more nuanced interpretations that fall into the purview of clinical practice guidelines almost assuredly will be revisited based on the newer results. And whether things remain a Class I indication per a different schema or go to another tier is something that we'll have to anticipate. But I definitely appreciate your comments.

DR. ALLEN: Well, I think the difference, too, for me is that if you look at some of the older literature and you compare how balloon pumps were used in a different era, when our therapies weren't as refined, we didn't have this sophisticated inotropic support, we didn't have better interventions, and now you look at applying these newer therapies in our current era, you know, balloon pumps may not work real well.

But not every program in the United States has access to all of these sophisticated therapies, and the balloon pump, in my opinion, and in my personal biases, is an easy tool to implement and support patients hemodynamically with.

DR. YANCY: Dr. Cigarroa?

DR. CIGARROA: So just as a follow-up, I think there's a distinction. We, I believe, all at this table would support the statement that intra-aortic balloon pump counter-pulsation improves hemodynamics. And that is whether it's due to a VSD, mitral regurgitation, or pump dysfunction,

we can demonstrate in those three broad categories of patients a reduction of the pulmonary capillary wedge pressure, reduction in preload, a reduction in wall tension that we believe translates to a clinical benefit in a subset of patients.

The challenge always is, at that moment, which patient will that buy you enough time so that the fix will work. And we would all, I believe, agree that identifying that patient group at present and distinguishing from the 40% that will die is quite challenging. So I would say it's efficacious. It's just hard to identify in the hard endpoint of myocardial salvage or change in mortality, that is death, the difference.

DR. YANCY: So the statement that I asked Ms. Waterhouse to portray for us is on slide 59. And there's a specific phraseology, Dr. Cigarroa, that says "to improve cardiovascular functioning." From your commentary, I believe you'd prefer it to say specifically to improve hemodynamics; is that correct? Or are you comfortable that cardiovascular functioning captures your intent?

DR. CIGARROA: I'm comfortable with it as it reads.

DR. YANCY: Okay. Thank you.

Dr. Yuh?

DR. YUH: Thank you. As a point of clarification, I do agree in principle to the reclassification, but for clarification with respect to cardiac surgery, is there a differentiation between the use of balloon pumps

prophylactically in cardiac surgery or all applications, including postcardiotomy syndrome, when you're struggling to get off bypass and you need to put -- we need some extra support during that time? It doesn't seem to differentiate that in the definition. I just wanted to make sure. I think it's everything, but I know that in the Executive Summary, most of the discussion is on -- and the study review is on prophylactic use in coronary bypass surgery.

DR. YANCY: If you'll look at the third component of the cardiac and non-cardiac surgery cleared indication, it reads, "Post-surgical myocardial dysfunction, low cardiac output." So I think that captures the statement.

Dr. Kandzari?

DR. KANDZARI: I'm going to be a little bit reiterative from my previous comments only because I'm not compelled by this statement. And my earlier comments were that what the device has proven to do is not upon what's represented in its labeling. It's for ACS or high-risk PCI or whatever it may be. These are all the clinical indications that you've mentioned that are challenged in the literature, but what the device does is improve hemodynamics. It doesn't necessarily improve cardiovascular functioning. As I interpret it, the ejection fraction may or may not get better, ventricular wall motion may or may not get better. We know that infarct size has not been convincingly, compellingly proven to be reduced by

this, but hemodynamics do.

And I would support the reclassification but with the discussion around the indication being an improvement in hemodynamic support with or without those labeled indications. And then we can also, as I mentioned, revisit including data in the product labeling that would help inform practitioners.

DR. YANCY: So in the spirit of continuing our discussions so we can reach closure, let's move away from acute coronary syndromes, consider that based on Dr. Yuh's statements, that we've addressed cardiac and non-cardiac surgery, and then briefly talk about complications of heart failure, unless I've overlooked someone who has a burning statement about the first two.

Dr. Cigarroa and Dr. Lange?

DR. CIGARROA: I'm still unclear about the non-cardiac surgery aspect. And the distinguishing using it prophylactically versus winding up in a difficult scenario and using it as a bailout to improve the hemodynamics and, again, buy you time. So, you know, the cardiac surgery, high-risk, diffuse CAD, inability to complete, you'll revascularize, going for a CABG, impaired function, you know, are certainly reasonable.

The non-cardiac surgery with just that statement, I don't quite understand the breadth of it or conversely the narrow focus, and I'm concerned about that.

DR. YANCY: Point well made.

DR. LANGE: The point so well made is the same one I was going to make. He just got to do it first.

(Laughter.)

DR. YANCY: You're slipping, man.

DR. ZUCKERMAN: So, Dr. Lange, what would you like that statement to say?

DR. LANGE: I'd like it to be stricken from the record. I mean, personally, it ought to be stricken from the record. The indication isn't non-cardiac surgery. That's too broad. We all have our cases where, oh, I had one or two cases where I saw this happen and we put a balloon and they live through it, and we have people who we've put balloons, and they died. But we don't attribute that to the balloon. So the question is: Are there data to support this, and in my opinion, there are not. But, again, that doesn't -- you're not modifying our practice. We can practice in any way we see fit.

And as David mentioned, these indications are so broad, you can just about classify anybody in this situation. If they have low output or hemodynamic failure as a result of non-cardiac surgery, then they could get it, but not prophylactically for non-cardiac surgery.

DR. YANCY: Dr. Yuh?

DR. YUH: I agree. That's one of those -- the non-cardiac piece is, like, what's wrong with this picture; you just pick it out, and it could easily

fit more consistently with the septic shock, you know, intraoperative pulsatility group.

DR. YANCY: I get a sense that the Panel members are in agreement with the theme expressed by Dr. Cigarroa, Dr. Lange, and Dr. Yuh?

DR. ALLEN: No, I wouldn't agree with that at all.

DR. YANCY: Dr. Allen?

DR. ALLEN: I think --

DR. LANGE: Could someone shut his mike off, please?

(Laughter.)

DR. ALLEN: I think to cut hairs, you could -- you have actually a really nicely done trial that doesn't support balloon pump use in cardiogenic shock and PCI. You can argue the nuances of it, but it's, bottom line, it's a very well done trial. We've heard a number of people say it. And the difference between septic shock and somebody with, for example, a perforated viscus with a critical left main that's going to an abdominal operation where he might have episodes of hypotension and vasodilatation because of sepsis, you actually are using the balloon pump in a way that it's physiologically designed to treat an underlying cardiac problem and stabilize that patient.

Its use in septic shock isn't at all facilitated by any mechanistic theories. And so I think there is a real distinction there. And when you look

at somebody that is having an emergent operation that has an underlying cardiac abnormality that the balloon bump has good animal and human data to support its hemodynamic use, to exclude that from its labeling I think would be a grave error on this Panel's part.

DR. YANCY: So just to press one step further, if that were removed from the record, struck from the record, how would that change practice the next time you see a perforated viscus in shock?

DR. ALLEN: One classic example would be -- and I realize we don't want to talk about reimbursement, but if CMS decides to follow pure labeling and I put that in a patient who has a perforated viscus with a critical left main, if it's not appropriately labeled, the hospital won't receive reimbursement, and the physician won't receive reimbursement for that, assuming it would go there. So labeling is important. And from a medical legal standpoint, labeling is also incredibly important. So it does change practice.

DR. YANCY: So the question becomes, does inserting this on the label imply that there's the same clinical experience or the same degree of evidence as befits the other statements that are there. It's just an open-ended question.

Dr. Brinker?

DR. BRINKER: So I think this is an exercise in semantics. Instead of having the all-encompassing statement as prophylactic for non-

cardiac surgery, if we had it for use in patients having non-cardiac surgery at extremely high risk of ischemia or hemodynamic decompensation, everybody would be happy.

DR. YANCY: So in order to complete our discussions --

Dr. Allen, if you can turn your mike off -- let's move on and have some brief feedback on heart failure, ischemic and non-ischemic --

DR. ZUCKERMAN: Dr. Yancy, I'm sorry to interrupt, but before we go on, could we just have a few more comments on Dr. Brinker's point, because our goal on slide 59 is to get away from these individual bullets and to have three, possibly, buckets. And are people happy with that second bucket that Dr. Brinker suggested?

DR. YANCY: So that's a little bit different, but we'll pursue that. Dr. Somberg?

DR. SOMBERG: I think, as Dr. Brinker, I think, is suggesting, is you use the intra-aortic balloon when you have problems related to ischemia, problems related to perfusion like shock, and then we're going to come to heart failure and low output syndromes. And whether that be in cardiac surgery or non-cardiac surgery or what have you, the basic hemodynamic area is important.

So that's one point I make. And the second point -- and I like the buckets -- the second point I make is that I think -- you know, I mentioned it before -- is we have to give -- not we but the FDA should, I

think, give attention to the fact that someplace in the labeling, it is appropriate to discuss that over time, our cardiac interventional procedures have changed. And depending upon what situation, different literature bases support the use or not the use of it.

So, for instance, if I was looking at a patient who was -- got thrombolytic therapy and fit the GUSTO scenario and was in cardiogenic shock or low perfusion state, or what have you, I think you would expect a dramatic benefit. If I had a patient who had PCI and was in shock, you would have to question at this point the database. That doesn't mean you don't use something, but you have to be frank, you know, write in your note, talk to the family, et cetera, you know, the chances of it benefiting; in a 600-patient study, there was less benefit.

So what you use this data on depends upon how it fits into the clinical scenario you're dealing with. But that's what it steps back from the issue of down-classification because these devices were approved 45 years ago like drugs were approved, some were used 45 years ago. Is their potency, is their utility the same? No. Do we constantly rewrite the -- or do we constantly either approve or disapprove the drug or device? No. But what we do is we modify the label. And maybe we should do that even more often.

DR. YANCY: So if we can make this more specific, let me come back to Dr. Brinker. If we were to consider a language change, what's on the

table right now is a request, first of all, to simply strike support for non-cardiac surgery, and that actually is in what would be slide 60. So it's not up there. So it would be cardiac surgery as opposed to non-cardiac surgery.

What also is on the table is to keep that there but to have the driver for all of this be hemodynamic support as may occur in acute coronary syndromes or as needed for cardiac and non-cardiac surgery.

Can you restate the approach that you would want us to take there, because those are our options, to either incorporate hemodynamic support or simply to strike that that's causing some angst?

DR. BRINKER: So I'd have to think this out a little bit. But the main issue is this is what the balloon does; it supports the hemodynamics. And you could make a blanket statement that it's indicated in those people with manifest hemodynamic instability or uncontrollable, unstable ischemia or thought to be at a high risk of developing such. And then that's all you would need probably.

DR. YANCY: Without articulating either of these other indications?

DR. BRINKER: Any of the other indications.

DR. YANCY: Yeah. I mean, that's a fundamentally major change from what's there. It is. But it does point out the hemodynamic support. We need more feedback on this particular issue. Let me remind the group where we've come so far. We've all agreed in principle that this is

clean for acute coronary syndrome, and it's primarily based on the wealth of experience, and we're comfortable with the reclassification.

We have a hang-up here with cardiac and non-cardiac surgery, and it's forced us to go back and revisit if the lead indication might not better be put as hemodynamic support in the scenarios of hemodynamic instability.

So let's get clarity of that and then move on to heart failure.

So I think Dr. Slotwiner would like to comment.

DR. SLOTWINER: Yeah. I just want to support the idea Dr. Brinker suggested of rather than being specific about the indications, be more mechanistic in the indications, I think particularly since there are so many situations which this covers right now, but we don't fully know which patients to use it on. And, clearly, it's a mature technology that's eventually going to get replaced. And I think that focusing on the ischemia, hemodynamic support, and patients who need that critically is a better way to go in the specifics.

DR. YANCY: We aren't yet answering the FDA's questions, but in the spirit of this conversation, I hope everyone starts to give some real thought now to how we'll be able to formulate a specific answer to the FDA questions because that will be required.

Dr. Kandzari, does this make it a more broad indication or a less broad? It seems like it's really widening now.

DR. KANDZARI: Well, I think our challenge has been that we've been tethered to these indications, and we're talking about cardiac support, non-cardiac support, acute ischemic syndromes, and I think if we just fundamentally -- so I think there are special controls that we'll discuss are satisfactory for the down-regulation of the classification.

But I also think that if we go to the hemodynamic support issue, the challenge that we also face is that we're not -- we're then opening up what FDA has recommended as a Class III clinical situation. That is, if we say broadly this is a Class II device for improvement of hemodynamic support and we don't mention for cardiovascular syndromes and/or heart failure I know you want to discuss, if we just leave it for hemodynamic support, we also then could allow open space for septic shock and IPFG. So I think there has to be some clinical scenario tied with it.

DR. YANCY: Dr. Yuh?

DR. YUH: Would it be too simplistic just to say cardiogenic hemodynamic stability? That should exclude septic shock, shouldn't it?

DR. KANDZARI: No, because septic shock can be --

DR. YANCY: Not necessarily --

DR. YUH: I guess it --

DR. YANCY: Dr. Hirshfeld?

DR. HIRSHFELD: Yeah, I guess I'm less concerned than the rest of the Panel is about the way the language came out originally. I think, first

of all, it's important that the indication language not become a blank check. And I think that's something that we've been discussing. But I think the solution to the conundrum is to actually combine the description language and the indication language into the indication because in the description language, you basically describe what it does and what it's for. And then in the indication language, as it's currently written, it's just a list of diagnoses and syndromes in which it's applied.

But I think what we're talking about, in essence, is that when you are in one of these situations where it's beneficial to improve hemodynamic performance or cardiovascular functioning, depending on which you want to do, this will do it. And so I think that if we lift some of the language from the description and insert it into the indication paragraph, we may cover our bases.

DR. YANCY: So we have several templates of thought here. And in the spirit of giving ourselves time to really think this through and completing our internal deliberations, let's have some pointed feedback on ischemic and non-ischemic heart failure so that we can get on to discussing the Class III indications as well.

Well, I may be the only person that lives in that space, so I'll tell you that I think in this scenario, the data are pretty adequate. None of the data are strong, but certainly, as a bridge device and supporting progression on to transplants and LVADs, I see no shortcomings here. And,

again, based on a wealth of experience, it appears to be more than adequate to include that in the Class II designation if that is what we so choose to do.

Dr. Hirshfeld?

DR. HIRSHFELD: Not as one who primarily takes care of these patients but as one is the implementer of putting these in those patients, I would second that. I think that there are times when these patients are so critically ill that they may not survive long enough to get whatever the next definitive step of therapy is. And this is something which is life-saving, to permit them to get to the next step, whatever that may be.

DR. YANCY: Thank you.

Let's move on to the Class III indications as recommended by the FDA. And this would be for septic shock and also for intraoperative pulsatile flow generation. And it would mean that for continued use of intra-aortic balloon counter-pulsation for those indications, it would require premarket approval.

Any thought, any feedback on these statements?

(No response.)

DR. YANCY: I'm assuming by the quiet that all on the Panel would agree that these are appropriate Class III and that means that they would necessitate a premarket approval.

Are there any other discussions the Panel would like to have about intra-aortic balloon use, intra-aortic balloon counter-pulsation, or the

use of an IABP before we go forward to the FDA questions?

(No response.)

DR. YANCY: Are there any points of clarification that you would like to reengage with the FDA either concerning the process we need to go through, the definitions that we are deliberating, or the device that we're discussing?

(No response.)

DR. YANCY: Hearing none, that puts us at a point where we can begin to look at the FDA questions.

Dr. Zuckerman, were there any things that you wanted us to discuss before we go over FDA questions?

DR. ZUCKERMAN: No, I think we're ready for the questions.

DR. YANCY: Okay. We appreciate that.

Let's give FDA two or three minutes to prepare for the questions, and then we'll resume at 20 minutes to.

(Off the record at 4:37 p.m.)

(On the record at 4:40 p.m.)

DR. YANCY: If we can all come to our seats, we'll get started momentarily. Thank you, Karen, and thank you, Dr. Zuckerman, for the clarification.

At this time, let us focus our discussion on the FDA questions. Copies of the questions are in your folders. I want to remind the Panel that

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've heard today, particularly this afternoon, and your individual expertise as we sit around this table.

With that said, once again we will request that when you speak to these questions, that you will take the time to identify yourself to facilitate documentation and capture in the transcription.

The reason for the brief pause was to make certain that we address these questions correctly, as the text that appears before you in print is different from the questions that we'll pose. And Karen will further highlight that nuance difference.

Karen?

MS. ULISNEY: Thank you, Dr. Yancy. This is Karen Ulisney from the FDA. For the final questions, those that are projected here on the screen are a little bit different, and that only reflects Question No. 2. So when we get to Question No. 2, I will point out the difference. And it is just a few different changes in the wording to the question itself and a subject of that question. So I'll get to that when we reach Question No. 2.

But to begin with, regarding Question No. 1:

The FDA has identified the following risks to health for intra-aortic balloon pumps based on the input of the original classification panel, review of industry responses to the 2009 515(i) order and the Manufacturer

and User facility Device Experience, or the MAUDE database, and FDA literature review.

We identify the risks as follows: Cardiac arrhythmias, ineffective cardiac assistance, thromboembolism, aortic rupture or dissection, limb ischemia, gas embolism, hemolysis, infection, insertion site bleeding, leaks of the membrane or catheter, balloon entrapment, insertion difficulty, failure of the balloon to unwrap, malposition of the balloon in the patient, vessel occlusion resulting in infarction of an organ, thrombocytopenia, and software malfunction.

Is this a complete and accurate list of the risks to health presented by balloon pump devices? 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 balloon pumps.

DR. YANCY: Karen, thank you very much. This is open for discussion. Dr. Lange is recognized first.

DR. LANGE: Should we also include death and stroke?

MS. ULISNEY: Death and stroke were not part of the risks identified with use of the device.

DR. LANGE: I realize they're not on this list, but I would include death and stroke as risks to health presented by IABP devices. In the presentation from the FDA, 3% of deaths were attributed to the intra-aortic

balloon pump, if I'm not mistaken.

DR. YANCY: And, certainly, we are prompted by the question to indicate if there are other risks that should be included in the overall risk assessment of IABP devices.

Any more feedback on including death and stroke on this list of risks to health for IABP devices?

(No response.)

DR. YANCY: Any disagreement?

Dr. Greenfield?

DR. GREENFIELD: Just to comment that I think we should recognize that vessel occlusion can result in ischemia without infarction, and ischemic changes could be a more likely complication than infarction.

DR. YANCY: Thus, so far we've heard two statements from the Panel that would modify this list. On the third bullet point from the end, it would be vessel occlusion resulting in ischemia or infarction to an organ.

Would that be satisfactory, Dr. Greenfield?

And then from Dr. Lange, we suggested the addition of death and stroke, and there were no dissenting opinions expressed.

Dr. Dehmer?

DR. DEHMER: I was just going to note that the fourth one down, fifth one down is limb ischemia, so in a sense it's already on the list.

DR. BRINKER: (Off microphone.) -- organs.

DR. YANCY: Any other comments about risk to health for IABP devices?

Dr. Naftel?

DR. NAFTEL: So excuse me. I'm sure that the wording has been thought through carefully, but this is just so weird to me. Risks to health presented -- I just don't get it. Why not say is this a list of the adverse events that a patient may experience who is treated with a balloon pump? I mean, what is this health thing? These are patients and it's adverse events. Isn't that what we're talking about? I mean, I just don't get it.

MS. ULISNEY: We're associating these with special controls that will mitigate the risks.

DR. NAFTEL: Yeah, but why not -- risk to health -- because I mean, I really have a point here. Earlier questions, it sounded like you were talking about public health or populations or something, and that's not what we're talking about. Am I wrong? Aren't these possible -- these are adverse events that may occur to a patient who has this balloon pump. Isn't that what this is?

DR. YANCY: Discussion on this point? Dr. Cigarroa?

DR. CIGARROA: I'll wait until this point is resolved and --

DR. YANCY: Discussion on this point, please?

Dr. Somberg?

DR. SOMBERG: I must say I see them as risks to health as well, so I think you can say it either way. I don't know why you're making a point of this.

DR. NAFTEL: I just don't know what health is. I know what a patient is, and a patient has adverse events.

MS. ULISNEY: I'm going to ask Christy Foreman --

DR. YANCY: So let's exercise our prerogative as an advisory group to indicate that we can share that suggestion with FDA and let them resolve where they'd like to go with that.

MS. FOREMAN: Hi, this is Christy Foreman. I'll try and address the issue to bring some clarity. When we identify the risks to health, it's the risk to health caused by using the device, meaning that these risks are things that we need to mitigate through special controls if we can. So, for example, when we say issues related to the balloon, what we're going to tie that to is if this is a risk of using that device and that the balloon could rupture, the balloon could become entrapped, we are going to have some bench testing that will assess the quality and characteristics of that balloon because we've said this is a problem that could occur from the device design and the device technology. So we need to be able to mitigate that risk. Certainly, you're dealing with sick patients and certainly you will likely have a mortality endpoint. There's not a lot we can do to mitigate the death of a patient who is very sick. What we are trying to mitigate are the risks of the device and

the things that we could reasonably apply special controls to to ensure that the device, when it complies with those special controls, is as safe and effective as a predicate device.

I don't know if that helps clarify it at all.

DR. YANCY: So I think that does help. Again, we're talking about, somewhat, phraseology, and there are some more specific points here about being more patient centric.

Dr. Cigarroa, you had another point you wanted to bring up?

DR. CIGARROA: Just to consider inclusion of compartment syndrome.

DR. YANCY: Any dissenting opinions to include compartment syndrome?

(No response.)

DR. YANCY: Are there any other additions, deletions, or modifications of this list of either adverse events or risks to health?

(No response.)

DR. YANCY: So with regard to Question 1, Dr. Zuckerman, this Panel believes that the risks to health or the adverse events of patients who receive intra-aortic balloon pump devices, based upon review of the available data, based upon input today from FDA advisors, and based on our own collective experiences, is reasonable with the following edits:

We would suggest including vessel occlusion resulting in

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ischemia or infarction. We would suggest including the following previously not articulated risks, that is, compartment syndrome, stroke, and death.

And the rest of it is acceptable.

DR. ZUCKERMAN: Thank you.

DR. YANCY: Question 2?

MS. ULISNEY: 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 or 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.

So the following is just a few edits to the language you have in front of you.

The FDA believes -- excuse me, here it is on the slide -- The FDA believes that longstanding, clinical experience coupled with available scientific evidence for IABP devices supports an adequate assurance of safety and effectiveness in the device's intended patient population for the following indications: acute coronary syndrome, cardiac and non-cardiac

surgery, and complications of heart failure of both ischemic and non-ischemic etiologies.

Even though some recent data demonstrates equivocal results, do you agree that the available scientific evidence and clinical knowledge is adequate to support the safety and effectiveness for IABP devices for these indications? And you can refer to the slide behind you if you need to look at that question again.

DR. YANCY: Go forward with b as well. Read b as well, please.

MS. ULISNEY: Certainly. Do the probable benefits to health from use of IABP devices for these indications outweigh the probable risks to health?

DR. YANCY: Thank you.

So this is the most important question of the day for intra-aortic balloon pumps, and it reflects our earlier discussion. And we had several statements that I'll remind you in context what we addressed.

One, we addressed the available database and discussed the equivocal findings in some recent trials. We heard one of our public speakers make specific reference to that.

Secondly, we all commented on the wealth of clinical experience.

Third, we all addressed the context of risk and benefit, given the underlying severity of illness in patients.

Fourth, we all discussed that the primary benefit was in improving hemodynamics.

And, fifth, we had some unresolved questions about the inclusion of non-cardiac surgery in the list of indications.

And then, finally, we thought about taking a minimalist approach and having the indication only read for hemodynamic support as opposed to articulating those that -- those indications that appear here.

So with that as our, if you will, preliminary thoughts, now we need to formulate answers to these questions. So with the statement as it reads, I need someone to take a first step at do we agree that the available evidence is adequate to support the safety and effectiveness for IABP devices for these indications. And as currently written, that's acute coronary syndrome, cardiac and non-cardiac surgery, and complications of heart failure, both ischemic and non-ischemic etiologies.

Dr. Somberg?

DR. SOMBERG: I say yes.

DR. YANCY: I think that's a good approach. We might start with a yes/no approach, and that might make life a little bit easier.

(Laughter.)

DR. YANCY: I just said let's keep that approach going. So there are others who feel that yes is the appropriate response. Dr. Doty, by a show of hands, says yes; Dr. Katz, Dr. Yuh, Dr. Allen, Dr. Kandzari,

Dr. Hirshfeld, Dr. Dehmer, Dr. Brinker, Dr. Greenfield, and Dr. Slotwiner.

So that would make it pretty clear that we support, in principle, that with all of the considerations of the device and our discussions about the data, in aggregate, we believe that it's sufficient to support the safety and effectiveness for IABP devices.

With regard to the indications, are we now comfortable that these indications as stated are reasonable and we accept this language, recognizing the FDA may modify in the light of our conversations earlier?

Dr. Cigarroa first and then Dr. Lange?

DR. CIGARROA: So I agree with the yes with the hope that the FDA would add some language to the non-cardiac surgery to address the issue of the "patient" who is at risk for hemodynamic instability or a large myocardial jeopardy score, something that protects against potential use of it in situations in which this Panel might not think would benefit it.

I do think there is a role in certain patients with non-cardiac surgery. I'm concerned, however, that at times it's applied where we might not utilize it.

DR. YANCY: Dr. Lange?

DR. LANGE: If you'd have picked me first, I'd have said that.

(Laughter.)

DR. YANCY: Are there others that would support that, in principle, what we see before us is acceptable but with a directive to FDA to

revisit the language that specifically addresses non-cardiac surgery. And whether that's a call-out of something more detailed about hemodynamics support would be something that would be developed over time. Is that fair?

Dr. Lange?

DR. LANGE: One other thing, I'd just like to reiterate my support of Dr. Kandzari's recommendation, is this is a good time to put in the latest literature to inform the people who use it of what it shows.

DR. YANCY: Point well made.

DR. ZUCKERMAN: Dr. Lange, that's Question 3, where we talk about using labeling as a special control and having truthful labeling. If we could concentrate on this critical 2a here right now, but we will get to that.

DR. LANGE: I just thought I'd bring that up before Dr. Yancy chose somebody else to say that.

DR. YANCY: He's been doing this to me for over 20 years.

(Laughter.)

DR. YANCY: It's important that we get some more feedback about this last component with regards to the indications. Are there parties around the table that are uncomfortable doing anything specific about non-cardiac surgery, recognizing that the data for all of these indications are, at best, equivocal or uncertain?

Dr. Somberg?

DR. SOMBERG: I could answer what you just said by yes because I am a little uncomfortable singling out non-cardiac surgery. It seems to imply that some non-cardiac surgeons are using it in a grotesquely inappropriate way. And I think we have no evidence or suggestion of that. What I think we have here is a whole host of indications that have developed over the years where people have had some clinical reasons, people are given clinical vignettes to that. And if we start singling out why should we write hemodynamic support for cardiac surgery; why don't we write hemodynamic support for congestive heart failure, for cardiogenic shock with PCI -- but you know, look at the SHOCK trial, and it may not work -- we could start making it so long that no one looks at it. I think the way it was written, it was very concise and appropriate.

DR. YANCY: More comments on this?

(No response.)

DR. ZUCKERMAN: Okay, Dr. Yancy, could I make one comment? As Dr. Somberg has just indicated, the most useful way for the FDA to regulate this class of devices as a Class II device would be to use this three-bucket approach. But one option, given the paucity of evidence regarding use in non-cardiac surgery, is just to delete the non-cardiac surgery and have it as acute coronary syndrome, cardiac surgery, and complications of heart failure, blah, blah, blah. If you could stimulate some discussion as to whether that option might be more preferable given the

database?

DR. YANCY: I promise you that is exactly what was about to happen before you spoke. And I was going to beat Dr. Lange to it.

(Laughter.)

DR. YANCY: But, again, in all seriousness, by a show of hands, how many persons around the table are comfortable removing "and non-cardiac surgery" and having that read "cardiac surgery" and going forward in that manner?

I see Dr. Cigarroa, yes, no? You want non-cardiac surgery to remain?

DR. CIGARROA: I want non-cardiac surgery to remain, but simply a proviso about in patients who are at risk for hemodynamic instability or large areas of ischemia.

DR. YANCY: Fair enough. Three votes. So I see Dr. Lange and Dr. Dehmer indicating comfort with removing it altogether; Dr. Slotwiner, that's three?

DR. SLOTWINER: But I would add some proviso to give some support for the concept, but remove it from this verbiage because it makes it -- it implies the --

DR. YANCY: So you're not in favor of removing it, but you're aligned with Dr. Cigarroa for some different language. And that's fine.

DR. SLOTWINER: Yes.

DR. YANCY: So either keeping it as is, removing it, or having alternative language. So, again, those that are in favor of just simply removing the reference to non-cardiac surgery and having it reading only cardiac surgery, how many Panel members are in favor of that, just simply removing the reference to non-cardiac surgery? I have one, two -- how many -- three. How many do I have that want to keep it just as it is; no changes? One, two -- so I have three for removal, two for keeping -- three for keeping it as is?

UNIDENTIFIED SPEAKER: Four.

DR. YANCY: Four now for keeping it as is; three for removal -- four for keeping it as is and at least two for alternative language.

Are there others that would vote for alternative language in the context of non-cardiac surgery? That's three, that's five, that's six. So six Panel members would vote to keep non-cardiac surgery but have some specific language about expectations or what would drive the use in that scenario; three would have it removed; four would keep the statement as is. And the Chair would vote for it to simply be removed. So that's 6, 4, and 4.

DR. LANGE: Can I call for a hanging chad vote?

(Laughter.)

DR. YANCY: Oh, dear. It's nearly 5:00 here, guys. I'm assuming, then, that as we've discussed before, we are in general aligning a and b, but if there's some specific language about Question 2b, I think we

can go ahead and develop that now.

(No response.)

DR. YANCY: Hearing none, then, Dr. Zuckerman, the opinion of this Panel is that in response to Questions 2a and 2b, the answer is yes, that after review of the available evidence in the context of broad clinical experience and understanding some of the recent equivocal data, there remains a feeling, the majority feeling by this Panel, that it is sufficient to support the safety and effectiveness of intra-aortic balloon devices for the indications listed, with a request that the specific indication of non-cardiac surgery be further developed to specifically address the necessity for hemodynamic support.

DR. ZUCKERMAN: Okay. Thank you.

DR. YANCY: Thank you.

And thank you to the Panel. I presume that that was amongst our more difficult deliberations.

Question 3, please, Karen?

MS. ULISNEY: FDA believes that the following special controls can adequately mitigate the risks to health for balloon pump devices for acute coronary syndrome, cardiac and non-cardiac surgery, and complications of heart failure of both ischemic and non-ischemic etiologies, and provides sufficient evidence of safety and effectiveness:

Appropriate analysis and non-clinical testing should validated

electromagnetic compatibility (EMC) and electrical safety; appropriate software verification, validation, and hazard analysis should be performed; the device should be demonstrated to be biocompatible; sterility and shelf-life testing should demonstrate the sterility of patient-contacting components and the shelf-life of these components; non-clinical performance evaluation of the device must provide a reasonable assurance of safety and effectiveness for mechanical integrity, durability, and reliability; and, finally, labeling must include a detailed summary of the device-related and procedure-related complications pertinent to the use of the device and appropriate warnings and contraindications.

Do you agree that these special controls are adequate to mitigate the risks to health for balloon pump devices for acute coronary syndrome, cardiac and non-cardiac surgery, and complications of heart failure, both ischemic and non-ischemic etiologies, and provide sufficient evidence of safety and effectiveness?

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. YANCY: Thank you, Karen.

Let me remind the Panel that reclassifying the device as a Class II device necessarily means that there will be a suite of special controls that will govern the use of the device in an adequate manner.

Based on our earlier discussions, the two things that are worth carrying forward are, one, the comment made by Dr. Naftel that this labeling doesn't necessarily infer or bring to mind the unique clinical characteristics that are involved. And the second, recently highlighted yet again by Dr. Lange, is how important the labeling must be in this spirit of a special control. And that was supported previously by Drs. Kandzari, Dr. Allen, and Dr. Somberg.

So with that as an introduction, let's have some discussion about the integrity of these special controls as being sufficient for the Class II designation: inclusions, exclusions, expansions, edits.

Dr. Somberg?

DR. SOMBERG: My answer to this question is yes. I think this is a very well-constructed list of special controls. And I think the last point, which Dr. Zuckerman drew our attention to, is the labeling. I think that it's really important and maybe a little unusual for a special control. But still, I think it's very important in light of what we've discussed today of the spectrum, from early very positive and later on less positive databases.

DR. YANCY: Let me press that last issue and turn to Dr. Lange. The statement as it reads says "labeling must include a detailed summary of device-related and procedure-related complications pertinent to the use of the device and appropriate warnings and contraindications." But it says nothing about the results of clinical trials or clinical expectations. Can you

comment on that, please?

DR. LANGE: I'd like to see those added. As Dr. Kandzari mentioned, I think it'd be valuable.

DR. YANCY: Is that agreement around the table? I think there's a consensus opinion that that would be an appropriate modification.

More feedback on the special controls as presented?

Dr. Naftel?

DR. NAFTEL: So I don't know if this is a given or not, but there's no data that we're asking for from the industry, and we're not asking for a post-approval study or anything like that. But we do have the MDRs. Can we, at least in a message to FDA, say will you formally annually look at the MDRs? And you may do this anyway. But, you know, for these devices, say, let's at least ask FDA to make use of what they have in-house just in case something weird is happening. That's why we have the MDRs. So can we write that in or suggest it as a formal annual review?

MS. ULISNEY: So part of the routine process through the MDR system is a review of the MDRs coming in, and there is a signaling process. So if there were an increased reporting for whatever the device, this included, this would be part of the signaling program. And this then begins a whole cascade of evaluation internally within the FDA; there are processes that we go through when these signals are alerting us.

DR. NAFTEL: So if I can push a little bit, because as we have

said so many times, MDRs are just numerators. Why not -- and maybe you have this plan in place. But why not ask the manufacturers for at least a count, how many got implanted each year, so rather than some nebulous signal, you could actually at least get some sort of rate? Why don't we make use of the MDRs as they were intended?

MS. ULISNEY: Well, they may not --

DR. YANCY: And just to add to that, I think what Dr. Naftel is getting to is the incorporation specifically of surveillance monitoring as one of the special controls using the MDR and maybe the IEPR as resources or repositories for that information; is that fair?

DR. NAFTEL: Yeah.

DR. YANCY: A response from Dr. Zuckerman, please?

DR. ZUCKERMAN: Okay. You know, again, postmarket surveillance can be utilized as a special control, but we'd like to hear more Panel input as to what the pluses and minuses are, and do we have value added in this particular situation, because, you know, just to clarify again, the MDR system stays intact. You saw what the numbers were over the last 10 years. Even with the problems that we know are part of the MDR reporting system, it still gave you a signal today. And do we need extra work or you know, so forth, so if other people could comment?

DR. YANCY: This is open because we're deliberating the addition of surveillance monitoring not through a postmarket surveillance

program, but using the already extant either MDRs from the MAUDE database or the IEPR.

Dr. Cigarroa?

DR. CIGARROA: My short answer is, yes, as written, with a change in labeling; no to any further surveillance.

DR. YANCY: Thank you.

Dr. Allen?

DR. ALLEN: Yeah, I would agree with Joaquin that the addition or the mandate for additional surveillance, to me, implies that the Panel has significant issues about safety. And if we have significant issues about safety, then we've answered some of the previous questions wrong. So I would say we don't have pervasions [sic] about --

DR. YANCY: So you agree with Dr. Cigarroa. So that's two parties that say keep the list as is and don't specifically include surveillance monitoring as a special control.

Dr. Greenfield?

DR. GREENFIELD: There is perhaps another way to obtain desired information about frequency of MDRs, and that is using MedSun, the HeartNet component of MedSun, which would allow you to track utilization as well as frequency of MDRs.

DR. YANCY: Dr. Somberg?

DR. SOMBERG: I just think it's not necessary to add that

verbiage in because this is the job of a large part of FDA is surveillance, and I've seen what that contributes to, how they're going to evaluate the performance of the device, whether there were any changes needed, whether there was labeling changes, et cetera. And to say that is sort of like saying do your job, so you know, I don't think there's too much evidence that they don't do their job. In fact, some people object to how much of a job they do, right? So okay.

And with that said, can I just raise one other issue? And that is drugs. Is there anything in the labeling --

DR. YANCY: Before we go to --

DR. SOMBERG: Okay. Got it --

DR. YANCY: -- another issue, let's just try to get some resolution. My sense is that enough parties are on the table that are saying that the systems in place are the systems in place and nothing else needs to be added.

Dr. Brinker?

DR. BRINKER: So I think that part of us are worried about that declassification will downgrade the kind of surveillance that is ongoing now. And it's true that it won't; is that correct?

DR. ZUCKERMAN: Not for required MDR reporting.

DR. BRINKER: So that's okay with me.

DR. YANCY: Any other comments about surveillance?

Dr. Somberg, you had a new issue?

DR. SOMBERG: Well, it's sort of a question in my mind is that over the course of the 45 years, pharmacologic therapy has changed drastically. I know when I was involved with intra-aortic balloons, we heparinized the patient. But now there's a whole host of antiplatelet therapies, antithrombin therapies, et cetera, et cetera. And I don't know this -- has anyone looked into it -- what are the best recommendations, what is the device compatible with, what does it require, what is it contraindicated with?

Really a question to FDA, and they don't have to answer it today, but that might be something that is of concern. I mean, I can see how being on some of the non-reversible anticoagulants could be pretty much an absolute contraindication to this thing inserted. I think you need to recommend the use of heparin. And what about, you know, double or triple antiplatelet therapy that some of these patients are on? Does that markedly increase the problem or decrease? So someone should look into this. And maybe you need to work with the device -- sorry -- the drug division on that.

DR. ZUCKERMAN: Okay. That's an excellent suggestion, Dr. Somberg, and we can add a device/pharmacologic interaction section. But for those who have used balloon pumps in the fibrinolytic era, et cetera, perhaps they can comment, because if you can get a good stick, I think the device has been used successfully with very powerful thrombolytics. But

perhaps the Panel can comment further.

DR. YANCY: We'll spend a brief period here. Before you speak, I just want to be certain that Dr. Lange doesn't want to go before Dr. Cigarroa.

(Laughter.)

DR. LANGE: I'm going to defer to Dr. Brinker and then agree. I know what he's about to say.

(Laughter.)

DR. YANCY: Okay. Dr. Brinker?

DR. BRINKER: So the one clear issue is it's not the device itself. It's the hole that we're concerned about. The device itself has a requirement, as we understand it now, for anticoagulation and absence of anything to prevent clot formation on it. But even that can be manipulated some.

The hole is remarkably well taken care of by a variety of techniques. And, in fact, the decreased size of the balloon shaft and the very pliable balloon material makes it possible for you to pull out the balloon without the winging that it used to have so that the hole is a minor issue and probably not dependent on the anticoagulation therapy that the patient has received although, obviously, the less -- the timing of anticoagulation and thrombolytic therapy, if it can be manipulated so that there's an absence of such when the balloon is taken out, it's best. But even if it can't, even if you

have thrombolytic therapy, you can do things to the site to buy you the time that you don't need to have a problem like a fem stop or something like that if you haven't pre-closed it.

DR. YANCY: It does appear that in the spirit of special controls, the conversation we're having now is more along the lines of the product information statements or --

DR. BRINKER: Right, well, I'm just saying that you don't need to worry about --

DR. YANCY: Correct.

DR. BRINKER: -- the thrombolytic.

DR. YANCY: Correct.

So if there are no other comments here, then what I'll say is, Dr. Zuckerman, in response to Question 3, the Panel believes that the special controls listed are reasonably appropriate to guide the use of intra-aortic balloon counter-pulsation for the indications of acute coronary syndrome, cardiac and non-cardiac surgery, and complications of heart failure, both ischemic and non-ischemic etiologies, with the one exception that the labeling be expanded to include clinical trial results and any statements that also address complications, warnings, and contraindications.

DR. ZUCKERMAN: Thank you.

DR. YANCY: No. 4, please?

MS. ULISNEY: The FDA believes that the safety and

effectiveness of balloon pump devices used to treat septic shock and intraoperative pulsatile flow generation is not well established. FDA bases its determination on the lack of sufficient evidence to support the safety and effectiveness for these devices, and therefore, FDA does not believe that special controls can be established to assure the safety and effectiveness of balloon pump devices for these indications.

Do you agree that the available scientific evidence is not adequate to support safety and effectiveness for balloon pump devices for septic shock and intraoperative pulsatile flow generation?

If you do not agree, please discuss the following:

The scientific evidence available in support of the safety and effectiveness of balloon pump devices for septic shock and intraoperative pulsatile flow generation;

And the special controls you believe that would be sufficient to assure the safety and effectiveness of balloon pump devices for septic shock and intraoperative pulsatile flow generation.

DR. YANCY: Thank you.

By a show of hands, the response to Question 4a, do you agree that the available scientific evidence is not adequate to support safety and effectiveness of intra-aortic balloon counter-pulsation devices for septic shock and IPFG? Please raise your hand.

Thank you.

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Dr. Zuckerman, in response to Question 4, the Panel unanimously agrees that the data are not adequate to support the use -- the safety and effectiveness for septic shock and IPFG; that would remain a Class III, and any further use would have to go for PMA.

DR. ZUCKERMAN: Thank you.

DR. YANCY: The Question 4b is no longer applicable.

Can you read the last question, please?

MS. ULISNEY: 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 balloon pump devices are life-supporting, which was supported by the original classification panel.

- a. Do you agree that balloon pump devices are life-supporting;
and
- b. On the available scientific evidence and proposed special controls, what classification do you recommend for:

acute coronary syndrome;

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cardiac and non-cardiac surgery;
complications of heart failure both ischemic and non-
ischemic etiologies; and
septic shock and intraoperative pulsatile flow
generation?

Finally, in accordance with 860.93, if you recommendation a classification other than Class III for any of these indications, please discuss the reasons for your recommendation.

DR. YANCY: Thank you, Karen. For Question 5a, do you agree that intra-aortic counter-pulsation devices are life-supporting? By a show of hands, yes?

Dr. Zuckerman, 5a, there is unanimous opinion of this Panel that IABP devices are life-supporting.

DR. ZUCKERMAN: Thank you.

DR. YANCY: For 5b, based on the available scientific evidence and proposed specific controls, what classifications do you recommend for the following, again, by a show of hands, acute coronary syndrome, II; cardiac and non-cardiac, II; complications of heart failure in both ischemic and non-ischemic etiologies, II; and septic shock and intraoperative pulsatile flow generation, III? Agree with those statements that I just made on behalf of the Panel?

Drs. Hirshfeld and Slotwiner, is that abstaining or you don't

agree?

DR. HIRSHFELD: Well, I'm sorry. I'm not sure. Are we voting on all four? Shouldn't we vote on each of these individually?

(Laughter.)

DR. HIRSHFELD: I'm sorry.

DR. YANCY: So we've been called on protocol. So on 5b(i), acute coronary syndrome, Class II, show of hands? Class III?

You okay with that?

5b(ii), cardiac and non-cardiac surgery, Class II? Class III? Yes, Dr. Slotwiner?

DR. SLOTWINER: I thought this was where we were going to consider other verbiage for the non-cardiac surgery.

DR. YANCY: That was earlier on when we were discussing indications. Now we're going by indication, Class II or Class III.

DR. SLOTWINER: Okay. Class II --

DR. YANCY: So let's do this again for clarity. 5b(ii), cardiac and non-cardiac surgery, by a show of hands, Class II? 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13. And then Class III? One.

And then for complications of heart failure, both ischemic and non-ischemic etiologies, 5b(iii), by a show of hands, Class II? And Class III?

So, Dr. Zuckerman, for acute coronary syndrome, it's unanimously a Class II. For cardiac and non-cardiac surgery, there is one

Class III vote; the remainder are Class II. And for complications of heart failure, all votes are Class II.

For septic shock and intraoperative pulsatile flow generation, 5b(iv), by a show of hands, Class II? And Class III?

So, Dr. Zuckerman, there is unanimity of this Panel that for septic shock and intraoperative pulsatile flow generation, it should be a Class III indication.

Now, let me remind the Panel that since we recommended a classification of other than III for a life-supporting device, we have to provide a rationale for that recommendation. The prevailing statements I heard during our deliberations were twofold: one, that there is a wealth of clinical experience that attests to the benefit of the device and, two, the specific benefit is in the improvement of hemodynamics in those patients that are hemodynamically unstable.

Is there a statement that anyone wants to make either to expand that or to incorporate that in some response to Dr. Zuckerman?

Dr. Lange?

DR. LANGE: To fulfill the letter of the law, also to mention that the special controls mentioned will mitigate the health risk associated with the device.

DR. YANCY: Thank you. I think I saw Dr. Yuh, Dr. Allen, Dr. Somberg; did you have comments?

DR. SOMBERG: He beat me to it.

DR. ALLEN: Yeah, he beat me to it. We just to add special controls. Look at that. You're right on.

DR. YANCY: So at least my visual field defects are equitable.

(Laughter.)

DR. YANCY: Dr. Cigarroa?

DR. CIGARROA: I let him beat me to it.

DR. YANCY: So before this changes or deteriorates any further, Dr. Zuckerman, in response to 5c -- and in all candor, this Panel acknowledges that we're giving a Class II status to a device that is life-supporting, and we're making a decision other than a Class III. But we believe that decision is driven precisely because of the special controls that we've deliberated and put in place and because of the wealth of clinical experience showing benefit and the important advantage of intra-aortic balloon counter-pulsation, to provide hemodynamic stability or protection from ischemia in precarious or unstable patients.

DR. ZUCKERMAN: Thank you. That's very helpful as a summary statement.

DR. YANCY: At this point in time, we need to obtain feedback from our industry representative and our patient representative. And I last started with Mr. Barrett, so I will start with Ms. Debra Gates McCall.

MS. McCALL: Let's see. My first experience with an IABP was

in 1982 with my mother and her MI. Since then, I've done multiple family members and friends, and I've been their primary caregiver. And I can cover MI, CABG, non-ischemic heart failure as well as the non-cardiac surgery to support heart failure. This has been very useful. I do like the additions for some of the indications, specifically because, as I've mentioned this morning, my mother's side of the family is morbidly obese, and so insertion site problems were rampant with them, whereas other family members and friends who were within a normal BMI did not have that problem. All of them had good results. So I think this is very useful.

And then, secondly, even though I realize this isn't the point of the Panel and of the FDA, I'd like to carry on with a point that Dr. Allen made earlier that creating some different verbiage, specifically, the buckets, which is a great term, if we're not careful with the verbiage and including things, that not only the hospital will not get paid, the physicians will not get paid, but sadly, that will become a patient burden.

DR. YANCY: Thank you for your comments.

Mr. Burke Barrett?

MR. BARRETT: Thank you, Dr. Yancy.

I was struck by one thing this afternoon, and it really started, the thread of the thought started when I was listening to Dr. Hirshfeld describe his tremendous experience with this class of devices, and in particular, when he described the evolution or the significant changes in the

technology over time.

And this Panel just reaffirmed that these are life-supporting devices. And we saw a very comprehensive review from the Agency when it came to MDR reporting and recalls. And at least what I'm hearing is as a class of devices, there aren't significant product quality compliance or adverse event concerns. And I think it's worth remarking and, for me, reflecting on the fact that while these devices have always been in Class III, that all of this occurred under the mechanism of the 510(k) and not under the mechanism of the PMA. And that did strike me today.

DR. YANCY: Thank you for your comments.

Even though this wasn't a conventional Panel meeting that addressed the question of approval or not, which necessarily means that each Panel member needs to articulate the reasons for their favorable or unfavorable vote, I think because of the nature of the issues we've discussed and anticipating discussions tomorrow, if there is a member of the Panel that would like to make a global comment, I think it's appropriate to enter that into the record, and we can set aside a few minutes for that.

So I'll start to my right and just by eye recognition see if anyone wants to offer any global comments, starting with Dr. Somberg, Dr. Yuh, Dr. Katz, Dr. Allen, Kandzari, Hirshfeld, Naftel, Lange, Dehmer, Cigarroa, Brinker, Doty, Greenfield, Slotwiner? Thank you.

I will simply add that there will be those that will look at what

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we did today and wonder how we made some of our decisions in the face of clinical trial data, recent clinical trial data that don't verify efficacy. And there will be those that will say that these are invasive devices and there are some complications. But I do think that this Panel did really great work today. We discussed with -- I think in a very thoughtful way and with great insight refining the indications. I think we discussed in a very appropriate way achieving clarity and consistency in the labeling of all devices, and that's through the course of the entire day, the morning session and the afternoon session.

And I think this Panel made it clear that we should begin to establish some levels of certainty about the effect or the expectation of these devices and set expectations accordingly in the context of the patients that are receiving the devices.

So I think we moved the clinical practice of cardiovascular medicine forward today. And I really wanted to thank the Panel members for your input and wish you well as you deliberate tomorrow.

Thank you very much.

We are adjourned.

(Whereupon, at 5:30 p.m., the meeting was adjourned.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

CIRCULATORY SYSTEM DEVICES PANEL

December 5, 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.

ZACH E. DUNCAN

Official Reporter