

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

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH  
MEDICAL DEVICES ADVISORY COMMITTEE

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CIRCULATORY SYSTEM DEVICES PANEL

+ + +

January 25, 2011  
8:00 a.m.

Holiday Inn  
2 Montgomery Village Ave.  
Gaithersburg, MD 20879

PANEL MEMBERS:

JOHN HIRSHFELD, M.D.	Chair
DAVID NAFTEL, Ph.D.	Voting Member
VALLUVAN JEEVANANDAM, M.D.	Voting Member
DAVID SLOTWINER, M.D.	Voting Member
RICHARD L. PAGE, M.D.	Temporary Voting Member
MAGNUS OHMAN, M.D., FRCPI, FESC, FACC, FSCAI	Temporary Voting Member
PAMELA E. KARASIK, M.D.	Temporary Voting Member
PATRICIA A. KELLY, M.D.	Temporary Voting Member
DAVID J. MILAN, M.D.	Temporary Voting Member
MYRON L. WEISFELDT, M.D.	Temporary Voting Member
RICHARD A. LANGE, M.D.	Temporary Voting Member
FRANK W. LoGERFO, M.D.	Temporary Voting Member

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THOMAS G. SIMON	Patient Representative
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MEETING

(8:00 a.m.)

DR. HIRSHFELD: I'd like to call this meeting of the Circulatory System Devices Panel to order.

My name is John Hirshfeld and I'm the Chairman of this Panel. I'm an interventional cardiologist from Philadelphia, and I'm affiliated with the University of Pennsylvania.

At this meeting, the Panel is here to discuss and make recommendations regarding the regulatory classification of automated external defibrillators, also known as AEDs. And the purpose of the Panel is to here reconfirm the current classification into the Class III, which makes these devices subject to premarket approval applications, or to reclassify these devices into Class II, which is subject to premarket notification under Section 510(k), as directed by Section 515(i) of the Federal Food, Drug and Cosmetic Act.

Before we begin, I would like to ask the distinguished Panel members and FDA members who are seated at this table to introduce themselves. So I'd like each person to state his or her name and area of expertise, and we'll begin all the way over on the left side. My left.

MR. DUBBS: Good morning. Bob Dubbs. I'm a patient advocate. I'm affiliated with a couple of different cancer centers, and I've served on grant review panels for NCI grants and I have served on one other

FDA Advisory Committee panel. And I live in West Palm Beach, Florida.

MR. BARRETT: My name is Burke Barrett. I'm the Vice President of Regulatory and Clinical Affairs at CardioFocus. I'm the Industry Representative on this Panel. I have almost 25 years of experience in Class III regulatory affairs, clinical affairs, and quality assurance. And it may be of interest to this Panel: I have run clinical studies on the sponsor side and prepared PMA submissions.

MR. SIMON: I'm Tom Simon. I'm a patient representative from Atlanta, Georgia. I have had atrial fib for 12 years. Fortunately, it was cured with radiofrequency ablation. And I've been on several panels in the past.

DR. MILAN: I'm David Milan, and I'm a cardiac electrophysiologist at Massachusetts General Hospital in Boston.

DR. KARASIK: I'm Pamela Karasik. I'm the Acting Chief of Cardiology at the Veterans Hospital here in Washington, D.C., and I'm an electrophysiologist.

DR. NAFTEL: I'm David Naftel. I'm a statistician in the Division of Cardiovascular Surgery at the University of Alabama at Birmingham.

MR. SWINK: James Swink. I'm the Designated Federal Officer for this Panel.

DR. PAGE: Richard Page. I'm a cardiac electrophysiologist and Chair of Medicine at the University of Wisconsin in Madison. I previously was a standing member on this Panel and came out of retirement for this Panel

today.

DR. SLOTWINER: I'm David Slotwiner. I'm a cardiac electrophysiologist at North Shore-LIJ and the Hofstra School of Medicine in Long Island, New York.

DR. OHMAN: My name is Magnus Ohman. I'm an interventional cardiologist at Duke in North Carolina, and I have expertise in clinical trial methodology, outcomes, research, and registries.

DR. KELLY: Patricia Kelly. I'm an electrophysiologist in Missoula, Montana.

DR. WEISFELDT: I'm Myron Weisfeldt, and I'm Chair of the Department of Medicine at Johns Hopkins. I've been involved with AEDs under the auspices of the American Heart Association for several years, and recently, as part of a resuscitation network that I'm the study chair for, for NHLBI, I've been writing up and publishing a number of manuscripts dealing with the efficacy of AEDs.

DR. LANGE: My name is Rick Lange. I'm Vice Chairman of Medicine, University of Texas, San Antonio, and my background is interventional cardiology.

DR. LoGERFO: My name is Frank LoGerfo. I'm a vascular surgeon at the Beth Israel Deaconess Hospital in Boston.

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

DR. HIRSHFELD: Okay, thank you. And if you've not already done so, please sign the attendance sheets there by the doors.

James Swink, who's is the Designated Federal Officer for the Circulatory System Devices Panel, will make some introductory remarks.

MR. SWINK: Good morning, everyone. I will now read the Conflict of Interest Statement.

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.C. Section 208 and Section 712 of the Federal Food, Drug and Cosmetic Act is 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 the Federal ethics and conflict of interest laws. Under 18 U.S.C. 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 services outweighs his or her potential financial conflict of interest. Under Section 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special Government employees and regular Government employees with potential financial conflicts when necessary to afford the Committee essential expertise.

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.C. 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 regulatory classification of automated external defibrillators, to either reconfirm to Class III, subject to premarket approval applications, or to reclassify to Class II, subject to premarket notifications, as directed by Section 515(i) of the Federal Food, Drug and Cosmetic Act.

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.C. Section 208 and Section 712 of the FD&C Act. A copy of this statement will be available for review at the registration table during this meeting and will be included as a part of the official transcript.

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

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 the FDA participant has a personal or imputed financial interest, the participant needs 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 January 25th, 2011, Thomas Simon has been appointed as a Temporary Non-Voting Member. For the record, Mr. Simon serves as a patient representative to the Cardiovascular and Renal Drugs Advisory Committee of the Center for Drug Evaluation and Research. This individual is a special Government employee who has undergone the customary conflict of interest review and has reviewed the material to be considered at this meeting. This appointment was authorized by Jill Hartzler Warner, J.D.,

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Acting Associate Commissioner for the Special Medical Programs, on January 24th, 2011.

Before I turn the meeting back over to Dr. Hirshfeld, I'd like to make a few general announcements.

Transcripts of today's meeting will be available from Free State Court Reporting, Incorporated, telephone (410) 974-0947. Information on purchasing videos of today's meeting can be found outside the meeting room at the registration table.

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

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

Thank you very much.

DR. HIRSHFELD: Okay, thank you, Mr. Swink.

We will now begin with the FDA Postmarket Update, and at this time we'll hear from the FDA speaker, Dr. Cara Krulewitch.

DR. KRULEWITCH: Good morning. My name is Dr. Cara Krulewitch, and I am a Branch Chief in the Division of Epidemiology, and I'm presenting for our Director, Dr. Danica Marinac-Dabic, on the post-approval study update.

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Just a little review about post-approval studies. We have a legal authority to conduct post-approval studies. They're clinical studies that are required as part of the approval order, and these are some of the code that goes with it. FDA may impose post-approval study requirements at the time of approval order, by regulation or subsequent to approval, and they may include continuing evaluation and reporting on the safety and effectiveness and reliability of the device for its intended use; other requirements, as FDA determines necessary and reasonable to evaluate the assurance of the safety and effectiveness of the device.

Post-approval studies are established to gather essential information in the postmarket arena for longer-term performance of the device, including the effects of retreatments and product changes, real-world device performance, including how the patients are responding as well as how clinicians are using the device, effectiveness of training programs, subgroup performance, and outcomes of concern that have been raised during the process of a premarket review.

Post-approval studies have a very strong public health value because they evaluate medical devices as they enter a real-world utilization. They contribute to better design of premarket studies and can provide infrastructure for nesting premarket clinical trials. They can detect real-time signals, which we then can take action on, help identify overarching regulatory science needs, and help prioritize CDRH epidemiologically research

resources.

Our division took over the program in 2005, and as we began to transition, there was an evaluation and a raising of the scientific rigor of the post-approval studies. And we have developed and instituted a tracking system, issued post-approval guidance documents, created a public health website, and initiated BIMO inspections for post-approval studies.

Over the last few years, we've also increased our focus on infrastructure building and focused on methods development as well as developing a post-approval transparency initiative and EPINet initiative that I'll talk about in a moment.

This is a picture of our website, and this is open to the public and posts all post-approval studies that have been issued since 2005. In addition, we have begun a transparency initiative that includes a newly expanded post-approval studies web page that went live on December 20th and has information on 173 post-approval study requirements ordered from January 1, 2005 to the present. The web page and its address can be found at the bottom there.

And the new fields that are included include post-approval study protocol descriptions, study populations, sample size for both the patients and sites, data collection, and follow-up visits. There's also a final data summary for completed studies and enrolled sites, finding strengths and weaknesses of the study as well as any recommended label changes. And

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we're still working and updating this as we speak, but this has gone live.

Over the course of the time that we've taken over the program, we have a number of original PMAs and panel track supplements, and this is the total for the whole program. As I said, there are about 173 now. In the blue is the number of PMAs that have been approved, and the red are those that are approved with a PMA. So you can see, it's about a third to a fourth of all studies, and it's been consistent. We really haven't increased the number over the course of time.

This is the number of post-approval studies, of PMAs that have been approved with post-approval studies, and sometimes there are a number of post-approval studies for each PMA. So you can see that as an example, in 2010 we have 13 individual studies for 8 PMAs that were approved.

We keep steady track of the progress of our post-approval studies, and right now we have 106 that are in compliance out of 139. The 33 out of compliance could be out of compliance for a number of reasons, including the adequacy of the progress of the study, the study may be pending, there may be revisions going on, and the like. But we do post that publicly, and that helps us to make sure that we're keeping on track for all of our studies.

Now, just a little bit in particular about cardiovascular devices. This is the number of the true cardiovascular device PMAs and panel track

supplements that have occurred over 2005 to 2010. And, again, blue is the number of PMA approvals, and the red is the number that were approved with a post-approval study. So it's been rather steady over the course of time.

This is the number of post-approval study applications and the individual post-approval requirements, and as you can see, oftentimes, with the cardiovascular devices, there appears to be more than one study with each of the PMAs that are approved. The majority of them are in compliance and on time.

So just a little bit about our post-approval study infrastructure building because we see this as a critical role and particularly the use of registries and device surveillance. Registries can provide product-specific device identification to the make and model down to the level and provide clinically rich information about the patients and the procedures and fills a critical void in the absence of unique device identifiers in automated healthcare databases. And it can act as a module in healthcare databases, sort of similar to enrollment files or pharmacy dispensing files and lab files which are used to track drugs.

We are working on a number of registry efforts, particularly for cardiovascular. We have the INTERMACS registry, which is an existing registry in surveillance, and we're facilitating new registry development such as the atrial fibrillation registry.

Additionally, we use registries for discretionary studies, such as the ICD registry, and we do explore registry capabilities, including active surveillance for short and longitudinal studies and potential linking to Medicare claims. And we have participated with the AHRQ guidebook and the compendium of pediatric registries as well.

I just want to talk a little about a fairly new project of ours, which is the MDEpiNet. This was created and supported by FDA and is a collaboration with academia and an epidemiology consortium to advance innovative methodologies for scientific computing and evidence synthesis based on the best principles of evidence-based medicine, comparative effectiveness research, and advances in health informatics.

Right now we have some pilot projects underway, and we just issued an RFI, which I believe is out. We are having an annual conference, it'll be our second annual conference, in April and we hope to establish some networks by April 15th, before the conference.

That's all I have to say. If you have any questions, thank you.

DR. HIRSHFELD: Dr. Zuckerman.

DR. B. ZUCKERMAN: I have a question, but any from anyone else from the Panel who would like to go first?

DR. HIRSHFELD: Would any Panel members have any questions they'd like to ask?

(No response.)

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DR. B. ZUCKERMAN: Okay, then let me begin because this is an extremely important presentation, Cara, and we're very thankful that you're here this morning. As you point out, over the last five years, the Center for Devices has really taken an active interest in beefing up its post-approval studies. But I have two questions that'll help the Panel in their deliberations today.

The studies that you're referring to are for Class III PMA devices (a) if you can confirm that. And (b) can you talk a bit about the 522 studies which can apply to Class II devices?

DR. KRULEWITCH: First of all, Dr. Zuckerman, yes, all of the conditions of approval, post-approval studies are for Class III devices, number one. Number two, the 522 study -- I wanted to double check, I had the exact criteria, so I do have them here -- can be for a Class II or Class III device for which failure of the device would be reasonably likely to have a serious health consequence, or it's a pediatric device -- there's four criteria -- or it's implanted in the body for more than one year, or it is a device intended to be a life-sustaining or a life-supporting device used outside of the user facility, which I believe we're talking about AEDs today, so that would apply.

We have a very detailed process by which we would issue a 522, whereby it would be initiated with what we call a 522 screener. We evaluate if any of those questions are matched, and then a group of subject matter experts are convened and they have a number of meetings to discuss

their concerns and issues, and we look at the device, we look across, based on literature and our MDR reporting system and any other information that's available to us, to make a decision of whether we will issue a 522 order.

That is an independent order that can be issued by FDA and will go specifically to all of the device manufacturers in that class. It can be by device or to the manufacturers in general. And when they get that order, they have 30 days to respond with a study to us, and then we will work interactively to develop protocols and have studies conducted. There is a time limit on those of three years once they are -- or 36 months for the study that will be done.

Does that answer your question, Dr. Zuckerman?

DR. B. ZUCKERMAN: Yes, that's very helpful.

And Dr. Lange, do you have a question?

DR. LANGE: Two questions just to follow up. One is, you presented the number of PASs. Can you tell us about the number of 522s? And the second question is, it's a three-year limit. Can that be extended?

DR. KRULEWITCH: I can answer the question more easily. By regulation, no, not under the order. I don't know if we can do it another way, but not -- the order is for those three years. I do not have the exact number of 522s. We can get back to you with that.

DR. B. ZUCKERMAN: Yes. Would it be fair to say, though, Cara, we do have a 522 page as well as --

DR. KRULEWITCH: Yes.

DR. B. ZUCKERMAN: -- a PAS page, and the number is considerably less? Dr. Tovar will be talking in a minute. And in our current regulatory scheme, we've had one 522 study in the AED arena, and he can describe that.

DR. KRULEWITCH: That's true. Thank you.

DR. KARASIK: Are the 522s pre-specified? It sounded to me like that was something that you could do afterwards. If the device is approved, it's a Class II, and now you want to have a 522 study. But can you say, at the time of classification, that you will mandate for a 522 study?

DR. KRULEWITCH: I don't think so. I think I don't have the correct answer to that regulatorily, but from my understanding, they are not pre-specified. They would be issued after the order. They're not a condition or part of an approval, if you're asking about --

DR. KARASIK: Yeah.

DR. KRULEWITCH: -- Class II devices. Yeah, that is one of the differences --

DR. KARASIK: Which is different than --

DR. KRULEWITCH: Right, a 522 is based on what we've observed --

DR. KARASIK: In response to something.

DR. KRULEWITCH: -- in response to a public health concern

about the device after it's on the market.

DR. OHMAN: Over here. So just to clarify that part.

DR. KRULEWITCH: Yes.

DR. OHMAN: So if you have an issue, whatever the issue might be, you're relying upon a layperson because these are, by and large, used among the lay public to report an issue so that you can respond and ask for more data, a 520. Am I correct in that sort of logic to this?

DR. KRULEWITCH: I'm not quite sure if you are or not.

DR. B. ZUCKERMAN: I think what Dr. Ohman is referring to, if I could rephrase it, is that generally with 522 studies, the way they evolve is that FDA has approved or cleared a device and then, through our passive reporting system, we have a signal that is raised. The Division of Epidemiology then needs to carefully look at the signal and see if it rises to the occasion of a 522 study, so that there are a lot of points in this pathway, Dr. Ohman. Would that be fair?

DR. KRULEWITCH: Yes. Not only our passive reporting system, but if through our regulatory epidemiology, which we are also actively doing, or other means, you know, that it isn't just the passive reporting system, but it may primarily be from those signals. We may identify signals from other sources as well, especially now that we have some of these collaborations with academia, where the signal may come through communications or concerns raised through academia as well.

DR. OHMAN: A second question, a brief one. Had the FDA reviewed the clinicaltrials.gov web page for identifying how many trials or investigations is ongoing with AEDs at this time?

DR. KRULEWITCH: I don't know. I can't answer that. I don't know about that. We may have. I'm sure that we have some epidemiologists working on that.

DR. HIRSHFELD: Dr. Page.

DR. PAGE: Yeah, thank you. I think this is a very important point, to be clear at least in my own mind, and that is, in terms of the Class II devices, the 522 process, that's in response to a specific signal, is that correct, as opposed -- so in other words, at least as currently written, Class II devices have no ongoing surveillance that isn't specifically attuned to an issue that's already been raised?

DR. KRULEWITCH: The passive reporting system applies to all Class II and Class III devices, but it is our passive reporting system. There is no mechanism by which we have studies ordered for Class II devices at this time, that's correct. There are some Class II devices whereby there have been voluntary studies that are being conducted. But we do not have regulatory authority to order a study on a Class II device except through the concerns raised by 522 that we observe when the device is on the market.

DR. PAGE: Great, thank you.

DR. HIRSHFELD: One more comment, Dr. Kelly, then we'll have

to move on to the FDA presentations.

DR. KELLY: Sorry, I thought I was clear on this, but now maybe not. So under the special controls, can you mandate a post-marketing study with a Class II device? So if the 522 is in response to a concern, I get that part, but can you just, under the special controls or the catchall, just mandate a study without having identified a particular concern?

DR. KRULEWITCH: Not once the device is approved. If you're talking about a special controls document, there can be language in the document to say we need clinical data for a device in order for us to approve.

DR. KELLY: So if today it were decided that this could be -- that AEDs could be reclassified as Class II devices, could you, today or when you make the final decision, put the special controls on right then and there?

DR. KRULEWITCH: I'm going to turn that back to Dr. Zuckerman to answer. That's more of a premarket question.

DR. B. ZUCKERMAN: Let's go through Dr. Tovar's presentation, when we look at the differences between Class II with special controls versus PMA, and you'll see how the 522 studies could fit in the bailiwick of Class II with special controls. So keep that question, and Dr. Tovar will be responding to it. But I think we're ready to move on, Dr. Hirshfeld.

DR. HIRSHFELD: Thank you, okay. And thank you.

So we'll now move on to the FDA presentation, and at the conclusion of this presentation, there will be ample time for questions from

the Panel members.

So we'll begin with the first FDA speaker, which is Marjorie Shulman. Or is it Dr. Tovar? Marjorie.

MS. SHULMAN: We're starting out well. Good morning. I'm Marjorie Shulman, and I'm with the Program Operations Staff, on the premarket notification staff, and this morning I am going to discuss device classification and reclassification.

So, basically, the devices were placed into two groups: there's post-amendment devices and pre-amendment devices. Pre-amendment devices were introduced to the market prior to May 28th, 1976, which was the Medical Device Amendments. Post-amendment devices are ones introduced to the market after that date, May 28th, 1976.

So the classification of pre-amendment devices. Back after the Medical Device Amendments of 1976, device panels and experts and the FDA sat down in meetings such like this and classified the devices into either Class I, II, or III, depending upon the risk of the device. Certain devices remained in Class III but underwent premarket notification until we either called for the PMAs or reclassified it to I or II. So that's what we're here today for. There were over 150. We're down to about the last 20. So we're slowly but surely getting all of these devices into the correct class.

So what happened was, we received a recommendation from a classification panel, we published the panel's recommendation for comment,

along with a proposed regulation for the device, and published a final regulation classifying the device.

So reclassification of pre-amendment devices can occur in a meeting such like we had in the late '70s, early '80s, in proceeding that parallels the initial classification proceeding, and based upon either new information respecting the device on FDA's own initiative or upon the petition of an interested person.

So post-amendment devices are automatically classified into Class III, and they remain in Class III and require premarket approval unless or until we reclassify the device into Class I or II, or we issue a substantial equivalence decision which classifies the device either into Class I or II, or the device is classified either into I or II via the evaluation of automatic Class III designation or also known as de novo review. So those are for post-amendment devices.

And reclassification of post-amendment devices can be initiated either by industry or FDA, and FDA, for good cause shown, can refer the petition to a panel such as yourself, and then the panel would make a recommendation to the FDA respecting approval or denial of the petition.

So there's three device classes, and a device should be placed in the lowest class whose level of control will provide reasonable assurance of safety and effectiveness. Class I is general controls, Class II is general and special controls, and Class III is premarket approval.

Class I mainly includes devices for which any combination of general controls is sufficient to provide reasonable assurance of the safety and effectiveness of the device. So general controls include, for example, prohibition against adulterated or misbranded devices, good manufacturing practices, registration of the manufacturing facilities, listing of the device types that an applicant would make in that manufacturing facility, record keeping, repair/replacement/refund, and banned devices.

Class II is for devices that cannot be classified into Class I, the general controls, 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 such assurance. So special controls include performance standards, postmarket surveillance, patient registries, development and dissemination of guidelines, tracking requirements, and recommendations and other appropriate actions.

Class III is for devices which insufficient information exists to determine that the general controls of Class I or the special controls of Class II are sufficient to provide reasonable assurance of the safety and effectiveness of the device, and such devices are life-sustaining and/or life-supporting, substantial importance in preventing impairment of human health, or present a potential or unreasonable risk of illness or injury.

So I just want to talk a couple seconds about restricted devices.

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Under the provisions of Section 520(e) of the Federal Food, Drug and Cosmetic Act, the FDA is authorized by regulation to restrict the sale, distribution, or use of a device because of its potentiality for harmful effect or the collateral measures necessary to its use; FDA determines that there cannot otherwise be reasonable assurance of its safety and effectiveness.

So a restricted device can only be sold, distributed, or used either upon the oral or written authorization by a licensed practitioner or under such conditions specified by the regulation. So if the device is restricted for use by persons with specific training or experience in its use or by persons for use in certain facilities, the Food and Drug Administration must determine that such a restriction is required for the safe and effective use of the device.

Devices such as cardiac pacemakers and heart valves, for example, require a practitioner's authorization. Hearing aids are restricted by a regulation which limits their sale to persons who obtain a medical evaluation of their hearing loss by a physician six months prior to the sale of the hearing aid, and the labeling of the hearing aid must provide information on the use of maintenance. So that was the basic background of the classification of medical devices.

DR. LANGE: It's not specified, but I just wanted to clarify. For special controls, that may or may not include manufacturing design and/or components as well as part of the special controls for Class II?

MS. SHULMAN: True. Class II devices are subject to design controls, which are -- that we do for the inspection, look at all the components for the device. For in the 510(k) and premarket notification, we do look at the finished device.

DR. LANGE: Okay, thank you.

DR. HIRSHFELD: Okay, thank you.

DR. SLOTWINER: Can I make just a question? I just want to make sure I understand. Can a Class III device be unrestricted in its distribution and sale?

MS. SHULMAN: Right, that can apply to either, any class, Class I, II, or III.

DR. SLOTWINER: So it could be unrestricted or no restrictions?

MS. SHULMAN: Right, correct. Thank you.

DR. HIRSHFELD: I think Oscar Tovar is next.

DR. TOVAR: Good morning. My name is Oscar Tovar, and during this presentation I will provide a brief background on the reclassification process. Next, we will present a summary of our pre and postmarket reviews. We will finish our presentation with a discussion of our preliminary recommendation for classification of AEDs. The Panel questions will be presented in the afternoon.

Our review team included reviewers for clinical studies, animal studies, human factors, hardware, software, basic electrophysiology,

surveillance, and compliance.

FDA began its regulation of medical devices in 1976 with the enactment of the Medical Devices Amendments. FDA categorized device types into one of three classes, as was mentioned by Marjorie, Class I, Class II, and Class III devices, as it was explained in the previous presentation. So I won't repeat here.

Because they were in commercial distribution at the time of the enactment of the Medical Devices Amendments of 1976, FDA allowed Class III pre-amendment devices to enter the market by submission and clearance of a 510(k) application. FDA intended to use the 510(k) process as a temporary measure for Class III pre-amendment devices. However, some pre-amendment devices, including automated external defibrillators, remained in Class III subject to 510(k).

FDA is now taking steps to issue regulations for Class III devices currently allowed to enter the market via the 510(k) process. Section 515(i) of the Act directs FDA to either reconfirm the devices in Class III or reclassify the devices into Class I or Class II.

The purpose of this meeting is to give the Panel the opportunity to provide a recommendation for the classification of automated external defibrillators by either reconfirming AEDs into Class III subject to PMA or reclassify AEDs to Class II or Class I subject to 510(k).

This table compares the premarket requirements under the

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current regulatory structure of 510(k) and PMAs. Bench testing and animal studies are reviewed under both paradigms. Clinical study design is dictated by the question of safety and effectiveness. In some clinical trials, it is possible to use well-established requirements and can be reviewed under 510(k). However, if there are new questions of safety and effectiveness, then FDA determines that the devices require premarket approval.

In premarket review of manufacturing information, we have the authority to request manufacturing information in order to make a determination of substantial equivalence, but this is not routinely done. However, there is a substantial review of manufacturing information in PMAs.

Preapproval inspections. We have the authority to perform pre-clearance inspections, but this is not routinely done under 510(k). Preapproval inspections, on the other hand, are routinely done under PMAs.

Review of any changes in manufacturing facilities. When such site changes introduce significant manufacturing changes, we have some authority to review the changes in manufacturing facilities, but they are not routinely done under 510(k). Manufacturing site changes are routinely reviewed under PMA. We have the ability to request 510(k) submissions for significant manufacturing changes, but they are not requested routinely, either. Manufacturing changes, however, are reviewed routinely under PMAs.

Postmarket surveillance studies, under Section 522 of the

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Federal Food, Drug and Cosmetic Act, are used in 510(k)'s to monitor the postmarket device performance. They can be ordered, as it was mentioned, if the failure of the device is likely to have serious adverse health consequences or for pediatric devices. These studies are very rare. I am aware of only one study, a 522 study, for AEDs in the past five years.

Post-approval studies can be required at the time of approval of a premarket approval to help assure continued safety and effectiveness of the approved device. Post-approval studies are frequent in PMAs.

Annual reports are not submitted under 510(k)'s, but they are reviewed routinely under PMAs.

The devices that we are going to consider for classification are AEDs sold by prescription. These devices are under the Product Code MKJ, which include semi-automated and fully automated defibrillators, monitor/defibrillators with AED mode, and AED accessories. We are going to consider also AEDs sold over the counter, these devices are under the Product Code NSA, and their accessories. I'm going to give a brief explanation of the type of devices in the next slides.

An AED is a device that automatically analyzes the heart rhythm and, if the rhythm is shockable, delivers an electrical shock to the heart to restore its normal rhythm, as an important component of resuscitation efforts. The AEDs can be semiautomatic, meaning that the device prompts the user to press a shock button if the heart rhythm is shockable. AEDs can

be also fully automatic. That means the user only has to apply pads to the patient. The device analyzes the heart rhythm, and if the rhythm is shockable, then the device delivers a shock without user intervention.

Then we have monitor/defibrillators. These are more complex devices and include monitoring capabilities, for example, electrocardiogram, oximeter, noninvasive blood pressure, end-tidal CO<sub>2</sub>, et cetera. These devices also include manual defibrillation and automated defibrillators. These devices are used by medical professionals mostly in hospitals and emergency medical systems.

The indications for use of AEDs. Automated external defibrillators are indicated for determination of a ventricular fibrillation and pulseless ventricular tachycardia. These devices are intended to be used on suspected victims of sudden cardiac arrest. Patients in sudden cardiac arrest are unresponsive and do not breathe normally.

The survival of a patient who has experienced a sudden cardiac arrest depends upon a sequence of events that include the successful delivery of a defibrillation shock. Other events that are included in the resuscitation efforts may include CPR, drugs, et cetera. The failure to deliver a defibrillation shock to a patient in ventricular fibrillation or pulseless VT can result in permanent injury or prevent the rescue of the patient.

All AED manufacturers submitted a reclassification petition or recommendation in response to the 515(i) order. These are the

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manufacturers that responded to the 515(i) order. One company in this list does not manufacture AEDs any longer and did not make any recommendation. All the other companies recommended that AEDs be reclassified from Class III to Class II subject to special controls.

The manufacturers responded with the rationale that special controls already exist to provide a reasonable assurance of the safety and effectiveness of AEDs based on testing to industry standards, guidelines, for example, the American Heart guidelines, device labeling, guidance documents, and postmarket surveillance.

In premarket review, we review clinical studies, animal studies, human factors, engineering, and in this case hardware and also software.

The clinical study design for new devices or new features, like sensors or algorithms, is determined by the clinical questions that need to be addressed. Some clinical studies are intended to reinforce, complement, or investigate relevant safety and effectiveness questions that can only be partially answered by preclinical testing. These studies can be reviewed under 510(k)'s. Some clinical studies, however, raise new questions of safety and effectiveness; therefore, these studies are reviewed under the premarket approval paradigm or PMA.

We review new defibrillation waveforms with novel shapes, durations, or shock intensities very different from currently cleared waveforms. The characteristics of a defibrillation waveform can have

significant effects on defibrillation threshold or for shock dysfunction. For example, a very low intensity defibrillation shock may not be sufficient to defibrillate patients with high impedance. Therefore, the waveforms require prospective, randomized clinical studies to provide data for the safety and effectiveness of the delivered therapy.

In these clinical studies it is possible to use well-established requirements and can be reviewed under 510(k). The requirements include successful defibrillation, restoration of spontaneous circulation, survival to hospital admission and hospital discharge. The sample size of the study typically includes approximately 52 subjects per group for the new waveforms and the predicate.

An area of active research, improved survival in sudden cardiac arrest, involves optimizing the delivery of defibrillation shocks and CPR. Optimizing the delivery of therapy during resuscitation efforts may raise new questions of safety and effectiveness. Therefore, these studies may require to be under the premarket approval paradigm.

User interface design quality typically cannot be achieved without involving users in the design and validation process and careful attention to their ability to successfully interact with the design of the user interface. The nature of use for AEDs lend themselves well to the simulated use testing and validation.

Therefore, we request manufacturers to provide the following

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as part of their submission: a sample device, final version of auditory instructions, labeling, carrying case, and accessories, and disc-based video recordings of the simulated use studies.

The level of human factors review on lay use AEDs is an essential element in the determination of the safety and effectiveness of these devices and is comparable to the reviews performed by programmable infusion pumps and left ventricular assist devices, as it was indicated by our expert in human factors. Although these reviews are not insignificant, AEDs for professional use required less testing and control.

Animal data is submitted either to support clinical studies or as standalone data to demonstrate the safety and effectiveness of a modified shock waveform, a new feature or a new device. New features include technology that can improve defibrillation and resuscitation, like new sensors, algorithms, et cetera.

Animal studies are also used to provide reasonable assurance for the safety and effectiveness of adult defibrillation waveforms attenuated for pediatric use. In some cases of new features, the application of the equivalence concept in 510(k) becomes very difficult because there is nothing to compare to.

Currently, FDA requests engineering testing of components in hardware and software as well as the compatibility of the changes, for example, electromagnetic compatibility, wireless consistent, and wireless

card systems. Bench testing includes the defibrillation waveform in the form of oscilloscope captures and waveform parameter measurements.

Performance standards provide test protocols with pass/fail criteria, which form a common language between manufacturers and FDA for substantiating claims so that we don't have to recreate the wheel every time. If a manufacturer chooses not to comply with an FDA-recognized standard, FDA reviews the adequacy of the test matters and results.

In the hazard analysis, hazards and mitigations are more similar to other devices that deliver therapy such as ICDs or wearable defibrillators, which are PMA devices. AEDs are software-based control devices. The software controls the hardware and is highly complex and unique to each device.

Software-based algorithms are critical to determine patient treatment, and they are more similar to treatment devices such as ICDs. The device testing in AEDs is unique to each device, and it's important as mitigation for device availability and readiness. Software design or implementation defects will result in patient harm.

Fast changes in technology make it difficult to apply the concept of substantial equivalence. For example, device characteristics that were cleared 10 years ago may not be adequate now.

Now Ms. Sullivan is going to present the medical device reports analysis.

MS. SULLIVAN: Good morning. This presentation is about medical device reports and AEDs.

In way of introduction and background, FDA and CDRH receive adverse events as medical device reports, referred to as MDRs. We receive them for both 510(k) and PMA devices. The regulatory authority is 21 C.F.R. Part 803. We receive reports that are both mandatory and voluntary. Most of the reports for AEDs come from manufacturers, about 98 percent.

A manufacturer is required to submit a report to us if their medical device may have caused or contributed to a death or a serious injury. Additionally, in the case of a device malfunction, if the malfunction were to recur and could likely result in a death or serious injury, that also is required to be reported.

MDRs are housed in a large database that we refer to as MAUDE, which stands for Manufacturer and User Facility Device Experience. If you go to our website, [fda.gov/MedicalDevices](http://fda.gov/MedicalDevices), you can see where the database is available online in an FOI version.

Looking at all of the reports for external defibrillators, about 80 percent of them are specific for AEDs. The remaining 20 percent are for the monitor/defibrillators, non-automatic, which are not going to be addressed here.

AEDs are classified by FDA as Product Code MKJ. This is just a chart of counts of reports for MKJ reports that we've received since 2005.

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You can see that the numbers have doubled from 2005 up through 2009.

I'll just mention, the year 2010 obviously just ended, and this is a preliminary number. I wanted to be able to give you a ballpark figure. But it looks like it didn't change much in 2010. But the increase is in that five-year period.

So an analysis was performed on the MDRs and the MAUDE database using the product code as the search criteria and date received by FDA between the beginning of January and the end of March 2010. Emphasis is on the report rate, device problems, and device evaluation. This ended up to be a total of about 24,000 reports.

The data was analyzed according to the event type by year, device problem code by year, manufacturer evaluation code by year, and confirmed component failures. Note that this data is provided in the reports by the device manufacturers.

Here's another chart that has the numbers of reports, but what I've done here is just break it out by the types of events being reported. You can see that the vast majority are device malfunctions. Very few serious injuries. Some deaths, which actually total about 900 in between 2005 and the end of 2010.

The small number of injuries is likely related to the nature of the device and the setting that it's used, patients in cardiac arrest. Many times the malfunctions are detected during routine device checks, whereas if

it's actually used, death may be an outcome.

Just to put it into perspective, if you're interested in the overall 2010, we received about 330,000 adverse events for all medical devices, and about 6,000 of those were for AEDs.

MDRs describe adverse events using one or more device problem codes. One MDR can have more than one code; therefore, the number can be greater than the number of reports. For purposes of analysis, the redundant codes were consolidated because there's lots of codes, and if they basically said the same thing, we grouped them. The by-year analysis showed a consistent increase in the number of MDRs among all the device problem codes.

This is a real busy slide. I'm not going to read it all. But the important thing to note is that it's ranked in order, the kinds of problems by year in descending order.

The top two problems make up over half of the reports that we received, and in terms of the ranking, you can see, if you just, you know, kind of look at the numbers by year, it really doesn't change. They're still the top problems. And 2010 is incomplete in this analysis.

The number one device problem reported was that the device displays an error message. Besides being the most common failure mode, over 40 percent of MDRs use this code. Nearly 20 percent of the death reports use this code. It's often accompanied by big narratives such as,

"During functional testing, the device displayed a 'unit failed' message. "

These are difficult or impossible to determine root cause or determine causal inferences based just simply on this information.

The second most common problem reported is failure to power up. This is the fastest growing problem code. These reports have nearly tripled since January of 2006. For example, "The customer reported that the device failed to power up," almost always the result of component or subassembly failure, not the battery.

Here's a chart showing, for all of the reports in the analysis, in ranked order, the manufacturer evaluation result codes. As you can see, the biggest number is blank. This represents the fact that the device was probably not made available to the manufacturer for analysis, where they can obtain any information about it. The next one is -- most common result was a component/subassembly failure. The third is other, which I don't know what that means. And the fourth is that the device performed according to specifications.

Two-thirds of time, reports did not have any manufacturer evaluation. Possible confounding factors are that (1) the device wasn't returned to the manufacturer. Also our reporting system, just going back to that, the manufacturers only have 30 days after they become aware or hear about a problem in the field to report that to FDA, and oftentimes that is not enough time to collect all the information and perform a returned product

analysis. So that information may come to us later in a follow-up report, and it takes a little more time to get that. The most common evaluation result was component or subassembly failure.

So looking at the component codes, a breakdown of those, when they were reported, this is the information that we have. Most common, a printed circuit board, then circuit board, cable, defibrillation subassembly, battery, transistor, connectors, switches, capacitor, display; a variety of components.

In conclusion, total reporting increased, more than doubled between the beginning of 2005 and the beginning of 2010. The increase is consistent among the event types and problem codes. Reasons for the increased number of reports cannot be determined conclusively. It can certainly be discussed and debated. It could represent, likely, more devices in distribution, more devices in use, more reporting by the manufacturers, or more device problems. You'll be hearing more about device recalls during this time period shortly.

Two-thirds of the failed devices don't report a root cause and are never evaluated by the manufacturer. Despite the high volume of reporting and serious nature of adverse events, MDRs do not include trend analysis or comparative data for even the most common failure modes. Annual reporting would improve overall surveillance by enabling FDA to possess trend data and distribution data, such as units sold, units returned for

cause, and units still in use, requiring reporting of manufacturing changes to gain a better understanding of the types of changes that are occurring and the reasons for those changes.

During this reporting period that was just described in the analysis, I would note that general and special controls for the device were in place. And you'll be hearing more about that as the day goes on.

I'd like to conclude and introduce my colleague from the Office of Compliance, Bradley Quinn.

MR. QUINN: Good morning. My name is Bradley Quinn. I'm a member of the Office of Compliance, and as much as ODE would want to you believe, we are a separate office from ODE, as noted on the agenda.

We're going to start by discussing the compliance analysis overview. We performed a postmarket data review of recalls, inspections, and regulatory actions taken, as well as discuss our current tools and our overall recommendation and discussion.

For the recall analysis, 68 voluntary recalls were conducted by AED manufacturers from January 2005 to August 2010. Seventeen of these were classified as Class I recalls, which are the most significant and above a reasonable probability of serious adverse health consequences or death. It should also be noted that of the nine manufacturers that responded to the call, six of which have had Class I recalls.

Forty-eight were classified as Class II, which is a remote

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probability, one was classified as Class III, which is not likely to cause, and two were classified as safety alerts, which involved a non-violative product and often involved communications about product enhancements.

This graph shows the number of recalls per year. Please note that 2010 ended in August, so it's an incomplete year. But as you can see, there's a slight increasing trend in the number of recalls.

Next, we'll move on to the quality system failures associated with the recalls. As a brief note, the quality system is a framework of procedures and practices for basic requirements used by manufacturers to ensure adequate design and manufacturing of devices. As you can see, these quality system failures included purchasing controls and receiving acceptance activities, design controls, production and process controls as well as process validation, and finally in-process and final acceptance activities.

I'd like to quickly note that there are a couple limitations on our analysis that was performed. Number one, there can be multiple and linked violations established. So, for example, you could have purchasing controls and receiving acceptance activities, but for the purposes of our classification process, we pick one, and also the information available at the time of classification may not always be complete.

Moving on to inspections, I'm going to start off by discussing the risk-based work program, which is an FDA method for identifying issues and trends in certain product areas to help better manage FDA resources. In

2006 AEDs were included in a risk-based work program. Four out of nine inspections performed as part of this program resulted in a classification of Official Action Indicated and the issuance of at least two warning letters, which we noted that the Official Action Indicated is the most significant recommendation for an inspection.

Continuing with inspections, as a general statement, AED firms are inspected more frequently than most other 510(k) devices. This is in part based on directed inspection requests and the risk-based work program assignments. Directed inspection requests are requests generated from the Center of the district offices who actually perform the inspections, and we direct them to inspect various firms for a variety of reasons, information that we have internally, and this often includes information from recalls that have just occurred or medical device reports that we have received. Furthermore, during these inspections, quality system deficiencies are also often identified.

Regulatory actions. Nine warning letters have been issued to AED manufacturers since 2005, citing issues in the quality system, as previously discussed; medical device reporting, from the previous presentation; corrections and removal, which is also known as recalls; and medical device tracking. Furthermore, it should be noted that there has been one consent decree, also known as an injunction, which is a judicial action where a manufacturer is required by law to stop production and address serious systemic quality system deficiencies.

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Within those warning letters, we have -- there's a common theme of the top five quality system problems. These include corrective and preventive action, also known as CAPA, complaint handling, design controls, nonconforming product, and purchasing controls and servicing tied for last place.

The current surveillance methods used by the Office of Compliance. We are often aware of problems through internal pathways or external complaints. These can include adverse events identified to the Office of Surveillance and Biometrics, design issues identified by ODE, whistleblower complaints, which often involve a member of the company providing information on that company, or trade complaints, where another company is providing information.

We also issue inspectional assignments or guidance to address the issues. These include routine inspections, which are part of the district's work plan for the year, and directed inspections, as I already mentioned.

As previously stated, it is during these inspections that we become aware of multiple problems. We often find serious deficiencies in the firm's quality system and also find safety issues that should be recalled by the manufacturer. It should be noted that voluntary recall may not occur until after discussion with the firms. These discussions may take months or even years after the company has known that the device is defective. Furthermore, you can also see a spike in recalls following an inspection.

In conclusion, the current general controls in place are not sufficient to ensure devices remain safe and effective. Issues identified with recalls, inspections, and regulatory actions occur after the AEDs have been manufactured and distributed using flawed procedures and processes.

Therefore, to ensure safety and effectiveness, we're recommending premarket review of manufacturing information including procedures and processes, preapproval inspections, and review of any changes in manufacturing facilities.

Using this information, the Office of Compliance can ensure that a manufacturer has adequate systems in place for tracking, trending, and taking appropriate corrective actions on potential safety issues once they have been identified.

We can obtain additional postmarket assurances through postmarket review of significant manufacturing changes to ensure that the changes are adequately evaluated and tested prior to implementation, and annual reporting of manufacturing changes to gain a better understanding of the types of changes and the reasons for implementation.

Thank you.

DR. TOVAR: Based on the data review and the current regulatory structure of the 510(k)'s and PMAs, our preliminary recommendation is that AEDs be classified as Class III medical devices and be subjected to regulations in accordance with premarket approval or PMA

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applications.

Now I am going to present Dr. Sapirstein, who has a different perspective that we would like also to consider for the classification of these devices.

DR. SAPIRSTEIN: Thank you and good morning. My name is John Sapirstein. I'm a Medical Officer in the Office of Device Evaluation, and I've been asked to briefly outline for you my thinking on down-classifying AEDs.

Now, let me just begin by stressing that this is essentially my opinion which I shared with colleagues at FDA while we were discussing the classification issue. It's an admittedly narrow perspective of a clinician and a reviewer, and as such, it really shouldn't be construed as a dissenting preliminary recommendation from FDA to you.

Commissioner Hamburg recently articulated what pretty much forms the foundation for my opinion, and though her comments, which I put up there, were made in regard to somewhat different issues, I do think they're also pertinent to the AED question. To paraphrase her, I'd say that in order to facilitate the development and review and approval of safe and effective AEDs, perhaps we may need to be a little bit more flexible.

Now, you've heard from the FDA presentation, arguably very valid justifications for why a Class III designation could be appropriate, and I don't disagree with them. But let me just list, very quickly, several potential

downsides that I can envision with the PMA -- excuse me, with the PMA being applied to AEDs.

First, as someone who's reviewed several of these devices and seen them used clinically, I've really been struck by the rate of change of device development and features implementation. And so I'm concerned that this pace of development might to some degree outstrip the time frame and requirements of a PMA review, perhaps leading to an unnecessary lag in a given technology's availability.

Furthermore, it would be incumbent upon FDA to appropriately analyze all of the increased data generated by the PMA requirements. And since resources are finite, even at the Agency, I'm concerned that this might further slow the overall regulation and availability of AEDs.

Second, there are requirements of a PMA submission, compared to 510(k), that in of themselves might discourage innovation and device refinement on the part of sponsors and developers. Now, some of these requirements are real and some of the burdens are just perceived by the sponsors. But in the end, I think it's important to acknowledge that the type of regulatory pathway that is chosen can to some degree affect what and/or when a device technology is presented to FDA.

And, third, I'll just say that the PMA is inherently a relatively inflexible paradigm, for instance, for requirements for both the sponsor and for the Agency. And this by design, obviously, and for a good reason. But it

may not allow for much regulatory latitude, if indeed such latitude were felt to be something beneficial.

Now, certainly there's precedent for FDA's embracing a non-PMA approach to device evaluation and follow-up for what otherwise might appear to be a Class III type or PMA type of device. A Humanitarian Device Exemption. An HUD program is what comes to my mind. I'm in no way suggesting that AEDs can fall under the HD regulations. Clearly they cannot. And it's not the Panel's or FDA's job, right now, to try and construct those new set of flexible standards of which the Commissioner spoke.

Instead, the question for me comes down to whether the appropriate use of the regulatory authority already contained under Class II designation might, on the whole, benefit the public health. That question led me to a sort of risk/benefit analysis, from which I concluded that indeed the answer may be yes.

And I'll get to some of the real benefits, if you will, of Class II over Class III in a minute, but let me first touch on the concept of risk, that a Class II might not provide adequate safeguards for patients needing these lifesaving AEDs.

Overall, I believe a Class II designation is sufficiently stringent to ensure the appropriate safeguards for AED use in the U.S. And, again, I want to underscore that my opinion derives from a narrow perspective obviously. That opinion did factor in the multi-disciplinary discussions we had

with the Agency on this topic.

The strongest safeguard in my view is that any Class II device must essentially first demonstrate to FDA's satisfaction that it is not a Class III device. In other words, it has to prove a negative. And of all the reasons why a device might not be considered substantially equivalent under 510(k), for me, the two most powerful ones are that it has an altered intended use or that there are new types of safety or effectiveness questions.

Now, if we believe the device under consideration has any of these, either of these characteristics or some of the other ones, it becomes Class III and is reviewed under the PMA process. Practically speaking, though, a Class III device never has the opportunity to prove its Class II characteristics to us, and thus, for the most part, once it's Class III, it's always Class III.

Now, if AEDs were Class II, special controls would be another essential safeguard in their review by the FDA. And you've already heard how some of the intricacies of AEDs may not lend themselves easily to the formulation of special controls. I agree that AED special controls would be very complex. But I'll point out some of the examples I've listed here that the Agency has successfully put forth special controls for many of the aspects involved with AEDs; now, except that in terms of complexity, the whole of an AED is going to be greater than the sum of its parts. But, nonetheless, I've yet to be completely swayed that AEDs are simply too complex for appropriate special controls to be generated.

And, finally, I'll just briefly bring up three benefits that I see from a Class II designation rather than Class III, understanding that others will certainly, I'm sure, disagree with my view of the extent to which these things can actually affect availability of devices for patients.

First, there's clinical data requirements for a new or a modified AED. Now, obviously having scientifically sound data is integral to what we do at FDA in reviewing devices, and it doesn't mean that all devices and device modifications need extensive clinical data to support their marketing.

Clinical trials, as we know, are very costly to perform, and they can take a long time to carry out. For the poorly designed or poorly executed trial, it does risk raising more questions than generating answers. And so clinical trial requirements do pose to a certain degree a risk of delaying, maybe even preventing, the timely introduction of new and good technology.

Now, it's true that the extent of clinical data required by FDA is to be driven by the device in question and not the type of review, i.e., the 510(k) or a PMA that it's undergoing. However, I do tend to believe that a PMA designation does in fact influence the type and extent of clinical data that both the sponsor and FDA expect for device submission. And I've put up some of the language of FDA's guidance that seems to me to intimate as much, and if you'll just read the sentence, "Most original PMAs and some supplements require clinical data," whereas, for 510(k)'s, "Clinical data are not required for most 510(k)'s."

Now, since special controls specifically provide for FDA to determine on a case-by-case basis what is an appropriate level of clinical data, I think that the Class II designation for AEDs may almost paradoxically lead to better clinical data, supporting faster availability of safe and effective AEDs.

Second, if one accepts that Class II safeguards can be rendered sufficient for the regulation of AEDs, it seems to me that actually doing so is really more consistent with FDA's least burdensome principles, a hallmark of which you can see there is "to encourage the timely development of new medical device technologies."

And, finally, I'll just make the comment that even the most well meaning of regulatory oversight or actions has the potential for setting in motion unintended consequences. One such consequence may very well be creating an environment in which there is a disincentive for sponsors to come forward with the types of design iterations that we really benefit from up to now.

So I'll conclude in this regard by pointing out that the substantial equivalence determination is intentionally focused, though it does have obvious safeguards in it. And perhaps, then, a Class II designation would make AEDs less prone to being subject to these unintended consequences, while at the same time giving FDA all the necessary tools and mechanisms to ensure the safety and effectiveness of the devices.

Thank you.

DR. B. ZUCKERMAN: Thank you, Dr. Sapirstein.

Before we proceed with Dr. Tovar's final comments, I just wanted to indicate one point for the record. Dr. Sapirstein has referenced an interesting *New England Journal perspectives* article that FDA Commissioner Hamburg has recently written. This should not be construed that FDA Commissioner Hamburg supports Dr. Sapirstein's position. In fact, she has not reviewed these slides. Thank you.

Dr. Tovar.

DR. TOVAR: Thank you. FDA understands the importance of maximizing the availability and innovation of AEDs for the public health. We understand that shortening the time from collapse to shock can increase the probability of survival of patients that have collapsed from sudden cardiac arrest, as well as the optimization of defibrillation shock and the resuscitation efforts, which includes CPR.

At the same time, FDA has identified serious postmarket deficiencies related to AEDs, arising from analysis of adverse event reports, AED recalls, and information from FDA inspections of manufacturers as they're being presented.

FDA has identified the following requirements as necessary to address these problems: premarket review of manufacturing information, preapproval inspections, review of any changes in manufacturing facilities,

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postmarket review of significant manufacturing changes, and annual reporting.

Now, going forward, this table summarizes how a reclassification to Class II 510(k) with special controls could look like and how a reconfirmation to Class III PMA would look like in a premarket review, that is, if we create special controls for each of these requirements.

Bench testing, animal studies, and clinical studies will be extensively reviewed under 510(k). This type of information will be reviewed the same under premarket approval. In premarket review of manufacturing information, we have the authority to request manufacturing information in order to make a determination of substantial equivalence, but this is not routinely done. However, there is a substantial review already of manufacturing information in PMAs.

Preapproval inspections. We do have the authority to perform pre-clearance inspections, but this not routinely done. However, preapproval inspections are routinely conducted under PMAs.

Manufacturing process changes. We have the ability to request 510(k) submissions for manufacturing process changes. This will require a promulgation of a guidance document.

For manufacturing site changes, when such a change introduces significant manufacturing changes, we have the ability to rely on guidance documents to tell manufacturers when these changes require a

submission. However, we have premarket review conducted and are eligible for inspections.

In postmarket surveillance studies, as was mentioned, and in the 510(k) with special controls, it is possible as interventional policy that we could have 522 postmarket surveillance studies. In premarket approval, we have preapproval studies or we could have also 522 postmarket surveillance studies.

Annual reports are not submitted under 510(k)'s, but they are routinely reviewed under PMAs.

If FDA were to reclassify AEDs into Class II subject to 510(k), the Agency would need to create special controls for each of these manufacturing and quality system requirements in addition to the special controls for engineering, software, human factors, animal studies, and clinical studies as proposed by the AED manufacturers.

The addition of requirements recommended for AEDs under 510(k)'s are already integrated in the PMA paradigm, and there is a lack of precedent for these requirements, the ones that I mentioned, as the special controls. Therefore, based on the data review and the current regulatory structure of 510(k) and PMAs, our preliminary recommendation is that AEDs be classified as Class III medical devices and be subject to the regulations in accordance with the premarket approval application.

Thank you.

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DR. HIRSHFELD: Okay, Dr. Tovar, thank you very much for your presentation.

And I'm pleased to see that we are ahead of schedule, it appears, which is good. We have some time budgeted now for the Panel to ask questions of the FDA and also to start some preliminary deliberations, and there's a lot to chew on in this. And so I would like to propose to the Panel, and I'd like to hear from the Panel back, a bit of an organizational structure for how we're going to approach this.

And it seems to me that right now there are two major concerns that FDA has raised. The first raised by Dr. Sapirstein was that the burdensomeness of switching -- of applying a PMA to this would potentially stifle the development of the AEDs in the future. And then the second is the concern that there's an issue of product quality, given the current regulatory environment, evidenced by the recalls.

And so I think what I'd like to propose to the Panel, and I'd like to hear other thoughts from the Panel if they have other ideas, is that we first focus on the issue of to what degree focusing to convert the classification to Class III would stifle future development of AED technology. And after we discuss that, we can then discuss the issue of to what degree there is a quality issue out there, in terms of the quality of the AEDs that are currently in the marketplace.

So I'd like to hear from the Panel before we start. I think that

would be a useful organizational structure, or if there's another organizational structure that the Panel would like to propose.

Yeah, Dr. Page.

DR. PAGE: Thank you, John. I think that would make a lot of sense. Before we do that, though, I think it would be worthwhile to define exactly what devices we're talking about today and how they're being used.

So if I may, I've been working with AEDs for about 15 years, back when we first started working with American Airlines and their defibrillator program, and I thought I understood the difference between an automated external defibrillator and an automatic external defibrillator up until this morning.

So I want to just clarify what we're discussing and what most of us think about as an AED. What I normally think about is a device that, in an automated way, recognizes a lethal arrhythmia, per package insert, is placed in someone who is clinically dead, unconscious, and that device will give prompts, either written or auditory, to a rescuer to push a button.

DR. TOVAR: Correct.

DR. PAGE: Today I was informed that since I first got into this, there is at least one device that is truly automatic --

DR. TOVAR: Correct.

DR. PAGE: -- that has already been approved, and this is a device that doesn't require that extra push the button, say, if the individual

says, I'm feeling better now --

DR. TOVAR: That's correct.

DR. PAGE: -- and the device would indeed shock in a way that it could only perhaps be overridden, but would automatically shock; is that correct?

DR. TOVAR: That's correct, yes.

DR. PAGE: Okay. We're not dealing with bedside monitors, except as they operate as automated external defibrillators, but those that do have an AED function we're discussing today; is that right?

DR. TOVAR: Right, yes. There are devices, complex devices, that have monitoring capabilities and also have manual defibrillation and automated external defibrillation, and these are used mostly in hospitals or in a system.

DR. PAGE: But the real key to this discussion, as I understand it, is the devices that are sold either over the counter or with a prescription or used typically by lay public in the setting of an out-of-hospital cardiac arrest. That's the crux of what we're really discussing.

DR. TOVAR: Right, right, yeah. Those devices are included, but also the monitor/defibrillator. Even the more complex devices with AED function are included in consideration.

DR. PAGE: I see, I see.

DR. TOVAR: Right.

DR. PAGE: And then finally, again, my background was with airlines, but I will mention this because I think it's relevant, is that frankly, on an aircraft, you have immediate response to someone who seemed to be unconscious and, as has been demonstrated, 40 percent survival of VF in the air. But when we reported it, half of those individuals had the AED placed in the setting of being not unconscious.

So at least by FAA, right now there are protocols out there for AEDs having a monitor that's visible, not a black box AED, but one with an EKG monitor. And the flight attendants, as we fly home, if we say we're feeling poorly and a health professional says, Put an AED on them, put a monitor on them, we'll have this monitor placed --

DR. TOVAR: Correct.

DR. PAGE: -- off label but consistent with FAA policy. And the final thing, and this is what I grow concerned about with some of the AEDs out there that can shock automatically, since we're not controlling how people use these devices, it raises some concern to me in terms of safety because in the documents one issue of safety is failure to convert. Another issue is potentially inducing an arrhythmia. One in ten of the failures that are listed on page 20, there's a 10 to 1, but still 82 inappropriate shocks reported.

And just for those who don't understand the concept, a well-timed shock on a normal heartbeat can, in worst case scenario, induce a lethal arrhythmia, which is another issue of safety for these devices that I

think needs to be considered.

DR. TOVAR: Right. Let me answer to that question. Yes, you are correct. There are devices that are fully automated, in which there is no user intervention. The device should be able to analyze the rhythm and determine whether that rhythm is shockable or not, and only if it is shockable, then the device will deliver a shock.

Now, in regard to your question about inappropriate shocks, I think maybe Mr. Luke Ralston that reviewed the MDRs could give us better insight into what that means in this case, because I'm not sure whether that is related to malfunction of the device in the analysis of the rhythm and then deliver a shock.

MR. RALSTON: Hi, my name is Luke Ralston, and I've been working in the Office of Surveillance and Biometrics. And first I would like to say that the point that you raised is a good one and that I think that the primary difference between these devices and the Class II defibrillators that we currently use is one of having the ability for diagnostics versus being used purely for therapeutics. And the ability to diagnose an arrhythmia is a whole separate and more complex issue.

The other question you brought up about possibly delivering an inappropriate shock, I'm speaking purely in the context of the MDRs that we read, but it is not uncommon -- in fact, I would say that it's more common than not -- that the narrative in the report states something along the lines of

the device delivered a shock when the clinician believed that a shock was not advised or vice versa. And in those issues, many times the problem is actually asystole, what determines asystole, because these devices are generally designed such that they will not shock asystole.

So if they do not deliver a shock because they've determined that the patient is in asystole and the clinician does not believe that that's the case, then we would get an MDR saying that it failed to deliver a shock in a rhythm that the clinician believes is shockable.

In the other case, which would be delivering a shock when the clinician does not believe it's shockable, perhaps Dr. Tovar or one of our epidemiologists may be able to speak more to the details of the studies that have been conducted over the years, about the sensitivity and the specificity of AED devices versus clinicians in general.

DR. PAGE: So those inappropriate shocks were generally in the setting of asystole or flat line and not in normal rhythm?

MR. RALSTON: A good number of them, yes.

DR. PAGE: I see.

DR. HIRSHFELD: Okay. I think what we should do initially before we discuss what I just brought up before is direct specific questions to the FDA presenters. So yes, please.

MR. BARRETT: I have a question for the FDA, probably best addressed by Mr. Quinn, but I'm not sure. It seems to me that the thrust of

the compliance presentation was that, at least historically, there have been quality problems in this field, at least with some of the devices and from some of the manufacturers.

My understanding is that many of the regulations that are available are the same, whether the device is in Class II or Class III. So the quality system regulations, which includes design controls, MDR reporting and recall, and so on, apply equally. And if I take it right, the thrust of your presentation is that if the devices are moved from Class II to Class III and we add this review of manufacturing in the PMA and we add the preapproval inspection, that the quality in the field will be improved. And I guess that's intuitive, but I'm wondering if there's evidence of that.

So, for example, these are complex devices with complex software. If you were to look at other Class III devices with complex software that have been regulated as Class III, where you have these other controls in the PMA, where you look at the manufacturing information, where you do the preapproval inspections, and you were to stack up, you know, with appropriate numerators and denominators, MDR reports and recalls, let's say, for pacemakers or ICDs, is there really a difference?

So I hear what you're saying, and to me it seems intuitive. I'm wondering if there really is a difference or if the controls that currently exist in Class II are adequate, and if this has more to do with the nature of the device and the design of the device and so on. That's what came to my head

when I was listening to your talk.

MR. QUINN: Sure. Yes, they are subjected to the same 510(k)'s, PMAs, quality systems, a quality system, 21 Code of Federal Regulation 820.

The main thrust of our Office of Compliance stance is that additional level of assurance that we would get by having those reviews up front as opposed to after it's already been manufactured and after it's already out in the field. We're looking to get it before it even gets to that point. So that's sort of where our recommendation is coming from.

So you did raise a good point with the ICDs and pacers. If you look at them comparatively, I mean, I'm not sure how those total numbers stack up, if one's high or one's the other. We do see significantly less recalls with ICDs and pacemakers. It's been awhile. I think we had a major thrust of recalls a couple years ago, five, six years ago. Since then there really hasn't been that many, whereas as you saw by the chart, we are continuing to see more and more AED recalls. So you've got your Class III PMA, 510(k). We do see less with the implantables.

MR. SHEIN: If I might, could I add something to that, Dr. Hirshfeld?

DR. HIRSHFELD: Please.

MR. SHEIN: Mitchell Shein, and I'm the Branch Chief for the Pacing, Defibrillator and Leads Branch in the Office of Device Evaluation.

Mr. Barrett, you made an interesting point, but you differentiated between asking for these things if we make them Class III. These are things that we've talked with the team and the people who weighed in on that within the Agency and we believe are necessary, regardless of whether they're Class III or Class II. The difference is, is that preapproval inspections are something that we have not routinely done in 510(k), but we believe they would be necessary perhaps as a special control for this product. They are already included part and parcel as part of the PMA process. So that is part of the regulation, and it's already in place and already done.

MR. BARRETT: So let me just make sure I understand it. I may have misspoke --

MR. SHEIN: It's okay.

MR. BARRETT: -- and mixed up saying Class III and PMA, and I meant PMA. But, then, what you're saying is at least two of the important things that you're seeking may still be available under Class II, under special controls, receiving some manufacturing information or more manufacturing information up front and the opportunity to inspect. You don't necessarily need to have a PMA to have the opportunity from a compliance point of view.

MR. SHEIN: That's correct. But it would have to be promulgated as special controls, either under guidance or as regulations.

MR. BARRETT: Thanks.

DR. HIRSHFELD: Dr. Ohman, did you --

DR. OHMAN: Yeah, this question may be mostly for Roberta Sullivan and Oscar Tovar. But I have two issues here, and one was what is the anchor here of events? You know, several thousands of events or reportings is sort of a high number, but the denominator of what is involved, you know, how many AEDs are out there, how many, you know, are being taken back because the batteries run out. I mean, there's a lot unknowns here, and maybe that is what you're trying to address by actually having some annual reporting so you can put this in perspective. But maybe you could help me with that.

MS. SULLIVAN: Our MDR reporting system is passive. We really don't have accurate numerators or denominators, and you can't get rates from it. We use it as a signal detection. You know, reports from healthcare providers are particularly valuable. But I would just say, I wish I knew the answer, especially with AEDs, what you use as a denominator as the device is manufactured, distributed, and used. You know, a lot of them don't ever get used; they just get checked.

So it's a good question. You know, I wish we had the answers. But I can tell you about the reports we get. The reports, 98 percent come from the manufacturer when they are aware of something that they need to report. There's things that happen that they're not aware of.

DR. OHMAN: And a follow-up question. One of the speakers

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referred to a 522 study that had been carried out. Maybe that was Dr. Tovar. But could you just share with us what that study looked like, what was involved in that part?

DR. TOVAR: Yes. The 522 study that just finished this year was about the over-the-counter AED. That was the Philips device that was cleared in 2004, and the Agency issued a 522 order to follow the performance of this device with actual users, and that's the only study that we have carried out under 510(k).

DR. HIRSHFELD: Dr. Kelly.

DR. KELLY: Can annual reporting be required as a special control if it's a 510(k), or no?

DR. TOVAR: If it is possible. I'm not sure whether we can do that. We don't have a precedent for that type of a special control. That would be a first time, a special control for it, yes.

DR. HIRSHFELD: Dr. Slotwiner.

DR. SLOTWINER: I noticed --

DR. LUKE: To address that question -- this is Markham Luke. I'm the Chief Medical Officer and Clinical Deputy for the Office of Device Evaluation.

If you're going to ask for lots of new things for 510(k)'s, you tend to further blur the line between Class II devices within the 510(k) program, and that we see as the overall problem. It's a problem for the

Agency and a problem for manufacturers. It doesn't provide clarity and predictability for devices as we see the classification schemes, Class I, Class II, and Class III. When you start merging all of those classes, that blurs the line for the public health, and that's an important consideration for the Committee to think about. Thank you.

DR. SLOTWINER: I have a question for Dr. Sullivan regarding the device evaluation. Slide 44. You said that 65 percent of reports, device failure did not have any manufacturer evaluation. Is that something that could be corrected if were Class III, or is that still going to be an elective process?

MS. SULLIVAN: Thank you, Dr. Slotwiner. I'm a nurse, but --

DR. SLOTWINER: Congratulations on the promotion.

(Laughter.)

MS. SULLIVAN: You know, that's hard for me to answer. It relates probably more to the field reps and the users of the device and getting -- you know, instead of keeping that device in use and just going on again, actually maybe taking it out of service, sending it back, getting to the root cause. If it's returned to the manufacturer, generally they're going to provide an evaluation result in a device failure mode. It just takes time, the device getting back.

I can't really address how that would change with a classification. Some of that's, you know, ongoing efforts that we have with

reporting quality. One thing in the last couple of years, reports have been coming in electronically, which improves the speed. You know, we're constantly working on the quality.

DR. SLOTWINER: Would these fall under the Safe Medical Devices Act and require reporting?

MS. SULLIVAN: Yes.

DR. SLOTWINER: So somebody is required to report it, but it's not clear who. I guess it could be the user who are not aware.

MS. SULLIVAN: Most of the mandatory relates to the manufacturers. They get a lot of complaints and then they evaluate them, whether or not they meet the reportability criteria that I mentioned before, caused or contributed to death or serious injury. Or a malfunction, that if it happened again, could result in a death or a serious injury. So they have to get a complaint, you know, screen it, does it meet the -- and then they have to report it.

User facilities have some obligations if they're aware of a death-related cause or contributed by a medical device, in terms of reporting that to the manufacturer and to FDA. But most of the mandatory is for the manufacturers.

DR. HIRSHFELD: Yeah, Dr. Lange.

DR. LANGE: Am I correct in saying that current hospital monitor/defibrillators, not AEDs, but hospital defibrillator/monitors are

currently Class II? Is that right?

DR. TOVAR: No, monitor/defibrillators are Class III. They are under the same product code, MKJ. The reason why AEDs, the ones that we see on the walls in airports and schools, and the monitor/defibrillators are included, is because our duty for reviewing classification of these devices falls under the regulation number and the regulation number, the C.F.R. 21, 870, 53.10, covers all of these devices under the same product code: AEDs and monitor/defibrillators, as well, the accessories.

DR. LANGE: So the MDRs we're seeing are both for AEDs and monitor/defibrillators?

DR. TOVAR: That's correct.

DR. LANGE: This is not unique to AEDs?

DR. TOVAR: No, no. It's not only to the ones on the walls. It would include also monitor/defibrillators.

DR. LANGE: So I'm really confused because --

DR. HIRSHFELD: Yeah, could we clarify this? Because this was different than what I had understood. I had been led to believe that standard hospital defibrillators were Class II devices and that we weren't lumping reports from those devices with the reports from on-the-wall AEDs. Can we make sure that we're absolutely clear on this?

DR. TOVAR: Right, I understand completely. The confusion is a little complicated. There are two types of devices, depending on whether the

algorithms analyze the rhythm automatically and then advise or delivers a shock. We have pure manual defibrillators in which the rhythm is displayed on the screen and somebody has to interpret that rhythm and, based on their judgment, to apply paddles in this case and deliver a shock to the patient, if it's necessary. Then we have the automated defibrillators in which the algorithm makes the decision.

And the algorithms can be in the devices that are on the walls and also in monitor/defibrillators because those are so complex and have so many capabilities, that one of the functions is automated defibrillators, if somebody chooses to use it. That's the difference.

The older defibrillators that have the automated algorithms that makes the decision are Class III, subject to 510(k) right now, under the Product Code MKJ. The manual defibrillators, the ones that don't have an algorithm to detect the rhythm, those are Class II already, are classified as a Class II under a different product code, LDD.

DR. HIRSHFELD: Okay. So what needs to be -- I think what the Panel needs to be clear on is that the MDRs that have been received include MDR reports from hospital-based, standard defibrillators that have automatic rhythm detection circuitry and the devices that are on the wall in the airport.

DR. TOVAR: Correct.

DR. HIRSHFELD: The data that we saw earlier is the lumping of those two groups of devices together.

DR. TOVAR: That's correct.

DR. HIRSHFELD: Is there any way that they can be separated so that we know whether this is a problem which is really confined to the airport defibrillators as opposed to the hospital-based defibrillators?

DR. TOVAR: Probably Robbie will be the best person to answer that question. Oh.

MR. RALSTON: At the risk of beating a dead horse, I think the delineation that we make, especially postmarket, when looking at these devices is that the LDD Class II devices that Oscar just referred to have no diagnostic function. So the line between what we would call a manual defibrillator has no diagnostic function whatsoever. It's purely therapeutic. And then, as soon as it incorporates any type of a diagnostic feature for the presenting rhythm, that's when we would begin to call it an AED. And the range of those is very large.

The monitor/defibrillators that we talk about using clinically usually can adjust the settings to be anything from a completely automated delivery of a shock to almost completely manual, where there is -- they can modify it such that it doesn't have a diagnostic feature.

And then, in addition to that, there are the publicly accessible defibrillators, or the PAD defibrillators, which one might see more commonly, say, like in an airport or a casino, where they maybe don't present the rhythm for viewing for the user. All they do is prompt the user to either deliver a

shock or not deliver a shock.

And then, between those two subcategories of AEDs, we currently do not have any type of a separate category for either one of those, if that answers your question.

DR. HIRSHFELD: Yeah, that does.

DR. LANGE: Just a follow-up. Obviously, let's talk about LDD devices for just a second. In other words, they're defibrillator devices without diagnostic capabilities. We're distinguishing just between whether it makes a diagnosis or not. Those must be associated with some MDRs. They must have some degree of component failure and they must have some manufacturing changes, waveform changes, et cetera, et cetera, just as the MKJs do. I guess what I'm interested in -- but those are Class II devices.

DR. TOVAR: That's correct.

DR. LANGE: And so are there special controls or is this -- obviously the only difference between the two is just the diagnostic capability.

DR. TOVAR: Right, that's a great question. The MDRs that you saw here presented today are only for automated external defibrillators. We saw a number of 23,591. And LDDs, for the same time period, were about 4,800 and something. Luke probably knows the exact number. But we're talking about 4500 MDRs for the same time period. And -- yes?

DR. B. ZUCKERMAN: Keep going, Dr. Tovar, and then I want to

continue, but continue with your thoughts.

DR. TOVAR: Yes. I'm sorry, I think I forgot the other question.

DR. LANGE: The question obviously is, one of the reasons for having a PMA is because of device failures and changes in components, changes in manufacturing, design, et cetera, et cetera, that require special controls. But the LDD devices that have everything other than a diagnostic capability obviously are prone to the same failures and the same changes, yet they're Class II.

DR. TOVAR: Right. And there might be some differences between the two devices. The Class II, as I said, are already classified. The AEDs, because they have the automated function, they were actually compared to monitors before. Now, we are in the process of the classification of these devices.

One of the differences can be the number of -- the numbers of the two types of devices that we have much more now, an increasing number of automated external defibrillators that we see in airports and schools, at public sites, and we have greater numbers of MDRs and failures that have been reported. As I said, the difference for the same time period is 23,591 for AEDs and 4,000 for LDDs.

Does that answer your question?

MR. SHEIN: If I could, specifically to your question? A 510(k) is considered a special control by the regulation, and that is in place. Excuse

me, a general control. We have not promulgated any special controls for the Class II devices. So they do not exist at this point, and we have not seen fit to call for those at this time.

DR. HIRSHFELD: Dr. Naftel has been waiting very patiently.

DR. NAFTEL: So a couple things. First of all, the MDRs. I've been studying them for years, and I complete the MDRs for 120 hospitals for ventricular assist devices. I think it's a great system. We're not making total use of it here because of what's bothering you, John, with lumping of these devices.

What we've been presented is quite useful, but I know, because on that form you ask, What was the device? Who manufactured it? So everything you've shown us could be split between the publicly accessible and inside the hospital. That information could be given to you if you wanted to source things out a little bit.

But I wanted to back up to the nice table that talks about injury, death, and other on these devices. When I deal with ventricular assist devices, when there's a device malfunction --

DR. B. ZUCKERMAN: Which slide are you on, David?

DR. NAFTEL: It's on page 19. It's that nice bar chart. Slide 30, I think, about.

DR. TOVAR: Is this the --

DR. NAFTEL: Yeah. Um-hum.

DR. TOVAR: Okay.

DR. NAFTEL: That's it. So when I deal with ventricular assist devices and there's the device malfunction, you know, there's not enough blood flowing and the patient likely dies, and it's easy for me to say that the device malfunction contributed to death. I had to admit, I'm getting a little confused here, though, because we have a patient who is in the process of dying.

So I'm just wondering, as you go through these MDRs and the reports and all the words -- and, you know, I can see that Form 3500A in my sleep. But you make a decision. Did the device malfunction contribute or potentially contribute to death? So am I saying that yes, the patient did die, or am I saying that the device malfunction caused the death? This is really --

DR. TOVAR: Yes.

DR. NAFTEL: -- really important to me as I think about safety.

DR. TOVAR: Yes, that's an excellent question because a device malfunction, sometimes there is no patient involved. The AEDs have self-diagnostic capabilities that runs diagnostics, some of them daily, some of them weekly, and some diagnostics are wrong, depending on the function that they are checking. And the devices sometimes detects by itself that there is a malfunction, and that malfunction is reported and never was a patient involved in some of these cases.

DR. NAFTEL: So what about where, though -- the column of

deaths, the row of deaths, can you tell me that the device -- are you ascertaining that the device contributed to the death or just was there while the patient was dying?

MS. SULLIVAN: Well, it's been submitted to us because the interpretation by the submitter was that the device may have caused or contributed. So there is a certain degree of being conservative, or not, in the reports, and that's understood. It's very difficult, you know, based on even -- well, there's the codes and then often accompanying, some narrative text. It's very difficult for almost anyone, as you know, in a clinical trial as these things will get adjudicated and --

DR. NAFTEL: Sure.

MS. SULLIVAN: -- it's not so much that it has to be a clear causal relationship between the device and the adverse event as somebody believed that it may have contributed or been a factor.

DR. NAFTEL: Would you be willing to make the unbelievably big jump that if the device had not been used, the patient would have lived?

MS. SULLIVAN: I think that's an important consideration, you know, in this kind of device. I also work with implanted defibrillators, you know, which is similar but different. But, you know, these people are in a state of cardiac arrest, and without any device, you know, they're going to die. So, you know, you have to take it in, you know, a clinical context in terms of that. But, you know, I can speak to the regulations and when reports

should be submitted. You know, as I think I mentioned in the presentation, it's very difficult to make causal inferences from these.

Since you submit reports to us, you know, that's just if you believe that there was a contribution or there may have been a contribution from the device, you know, maybe you don't know because you don't know if it wasn't used right or if the battery is broken or this or that, you may not know at that time, but because you have a suspicion that maybe the FDA should know about it or needs to know about it, you're submitting a report to us.

DR. HIRSHFELD: Mr. Simon, you've been waiting patiently.

MR. SIMON: Being a former atrial fib patient and a layperson, I'd like to follow up on Dr. Page's comment with regard to the use of the AED.

Do AEDs differentiate between A-fib and ventricular fibrillation? Whether they do or they don't -- and I should say whether they do or they don't, if the layperson applying that to an A-fib person and they applied it, would that result in anything other than putting them back in rhythm, or could it cause death or anything to that extent?

DR. TOVAR: Yes, let me see if I understand the question. You are asking whether the device can discriminate between atrial fibrillation and ventricular fibrillation?

MR. SIMON: That's the first question, yes.

DR. TOVAR: Yes. The device is trained to detect ventricular

fibrillation and very fast ventricular tachycardia, and those are the rhythms that are going to be trained in automated mode. However, if it is used in manual mode, then the physician is able to do the diagnostic and treat it accordingly, either a cardioversion or a synchronized delivery of the shock.

MR. SIMON: Right. But if it were to be applied to a patient who had atrial fib, what would be the result?

DR. TOVAR: It would depend on the rhythm. The algorithm of the device has certain parameters that detects heart rate, amplitude. It's a lot of the signal and the consistency of the signal. Those are the characteristics that tell the device whether this is ventricular fibrillation or not, or the device is detecting a ventricular tachycardia. But for A-fib, only if it fell -- only if the rhythm fell within those parameters, probably it would be -- then a shock would be delivered. But I don't know if somebody else has --

MR. SIMON: I guess I'm asking, if the layperson were to override and hit the button, what would result? Would it bring the A-fib person back into rhythm?

DR. TOVAR: Well, they aren't supposed to act, and the device isn't supposed to respond in that way.

DR. HIRSHFELD: And these are intended to be applied to unconscious patients.

DR. TOVAR: Right.

DR. HIRSHFELD: Dr. Jeevanandam has been waiting. He missed

the introduction. Dr. Jeevanandam is a cardiothoracic surgeon at the University of Chicago. So you had a question?

DR. JEEVANANDAM: Yeah, I just want to go back to that slide that Dr. Naftel went over. So I'm looking at, you know, malfunctions versus death. So if these patients are fibrillating and you put the device on them and then the device at that point malfunctions, in that it doesn't charge or there's a battery problem or there's a device problem, I would think that hadn't contributed to their death but hasn't saved them from death. So if there's a death involved, I think that would be contributing to the patient's death. I don't think, you know, it's causing their death, but it's preventing -- the malfunction of the device preventing their death.

Now, all the other malfunctions probably don't deal with the patient. If they're all self-testing, and if a device self-tests and finds out that it's defective, that's not really a malfunction; that's a built-in safety feature. The device is telling them to replace that device.

So, you know, if a device self-tests and it says the batteries are low or the batteries need to be changed, then that's actually a good thing, right, because that means that the devices need to be changed. So I don't know if all of the malfunctions there, if they are induced by self-testing, are actually adverse events as opposed to a device that's just testing itself, saying yeah, I'm not working, replace me.

DR. HIRSHFELD: Maybe if someone from FDA can address it

because I think Dr. Jeevanandam's point is an important one. Are what we are calling MDR reports, are they actually just reports of successful self-tests that said the device was not functioning properly?

DR. TOVAR: Right, but we have to take into account that if the device, for example, detected a resistor, that is important. If the delivery of the shock is not functioning, that device is not ready for the next -- for a rescue. That's why it is reported as a malfunction. Because it is true, the device detected the problem, it functioned as designed, but it's because there is something that is not working correctly on the device and the device won't be able to work properly in the rescue.

DR. HIRSHFELD: But this category of failure is what some of the industry refers to as up-time issues, in terms of whether or not what fraction of the time that a device in service is actually operational and functioning properly.

And so I think Dr. Jeevanandam's question was, are we detecting small times when a given device is not up but would be considered to be within the standards of any complex device for being able to be in service? Or are we actually detecting device malfunctions that are dangerous to people's health?

MR. RALSTON: I think that the point you're raising is one of the critical ones postmarket, which comes down to our definition of malfunction and death. And I have been the primary reviewer for these product codes for

a little over three years now, and from my own experience, almost about 90 percent of malfunction reports occur when no patient use is involved. And so they're self-tests when either a clinical engineer or perhaps a nurse or a clinician at the change of rounds determines that the device isn't working anymore.

But the same problem also occurs with, say, like the death and injury reports, where a very substantial minority of death reports, the narrative will state that this X problem occurred with the device and the patient expired. However, further interview with the clinician determined that the device was not responsible for the death.

Now, whether that's because maybe the patient was already in asystole or in a non-treatable rhythm is not usually specified, especially considering that, I think, the normal outcome of defibrillation two-thirds of the time is death, even if it's done correctly. So I think the issue that you're bringing up is important, although in the issue of malfunctions, it's primarily the malfunctions are occurring when the patient is not being treated.

Does that answer your question?

DR. HIRSHFELD: Dr. Zuckerman and then Dr. LoGerfo.

DR. B. ZUCKERMAN: Actually, can we reverse the order?

DR. HIRSHFELD: Okay.

DR. B. ZUCKERMAN: Dr. LoGerfo has been waiting for about 15 minutes. And then I'd like to say something.

DR. HIRSHFELD: I thought you were pulling rank.

(Laughter.)

DR. LoGERFO: Thank you. It would seem with the hospital device, when an incident occurs, there's a very precise record in many ways, written records, monitor records, and so forth, and I would assume that the reporting back to the manufacturer from those devices is very consistent. Perhaps I'm wrong, but I would make that assumption.

With regard to the AED alone, we have no record of exactly what happened. As far as I know, I haven't heard that any of these devices will produce a report of what happened at the time the shock was delivered. And so in that case, how do we ever know that these devices made a difference, if we don't know exactly what it did?

MR. RALSTON: Just to make sure that I understand your question, you're asking, how do we verify that what the manufacturer is telling us in their report is indeed what happened during the event? Or is there any way --

DR. LoGERFO: Can the manufacturer discern this? I mean, maybe they can debrief the device in some way.

MR. RALSTON: Well, many times they do interview the clinician on the scene. That does seem to be especially prevalent in the death reports where, if the clinician does happen to state that the device -- you know, the patient expired but the device was not an issue in the death, they'll include

that even though they've submitted it as a death report.

DR. LoGERFO: I can assure you that if I was a clinician in that situation, you cannot count on me to discern between rapid AF, just normal tachycardia, or ventricular tachycardia. So I don't see that the precision is necessary here. For this device to work, it has to be that it precisely identifies the arrhythmia and delivers the shock at the appropriate time.

And is it correct to say we have no record that any of these devices have ever done that? A hard record.

DR. B. ZUCKERMAN: Okay, Dr. LoGerfo, I think you're making a great point which really summarizes a large portion of this very rich discussion. Number one, we do have important clinical data supplied by people like Dr. Weisfeldt in a PAD trial, and Dr. Page, that these are important life-sustaining, life-supporting devices. However, our ability to generalize, then, in the real world is currently limited with the Class II system that we have passive reporting.

The Panel has done a good job of dissecting out what can be really made of these MDR reports, how sure we are, et cetera. And I would just underline that this is the reason why the FDA, in summary, has Slides 74 and 75, because certainly if you or others think that post-approval studies are an important part of maintaining an appropriate safety network, it helps you organize your thoughts as to what might be an appropriate class. Right now, with our current regulatory structure, these are the best data we can give

you, and we struggle with these data.

DR. HIRSHFELD: Thank you. Dr. Lange.

DR. LANGE: Again, just so I understand, help me to understand why LDDs are acceptable as Class II and AEDs need to be Class III. Again, because LDDs have the same components, the same potential failure rates, they have to go under the same monthly testing, they oftentimes come up short. And so help me understand why they're different.

DR. TOVAR: Right. One of the most important reasons probably is because LDDs are going to be used only for -- only by professionals and in a setting already where, if the device fails, either you have the option of another device or somebody can deliver CPR and buy time until you get another defibrillator.

With AEDs, especially with the ones that are used in public access defibrillation, if the device fails, then there is no other alternative. And that's what we're trying to improve, that these devices are ready and available for a rescue attempt. That's probably the biggest difference.

DR. HIRSHFELD: Dr. Milan.

DR. MILAN: So I have a question for Dr. Sapirstein, if I could. You made a pretty good case, I think, that maybe classifying these devices as Class II might encourage innovation. It's kind of a two-part question. One is, we've heard that if these devices were reclassified as Class II, there would be a lot of special controls that might be additionally applied to the 510(k)

mechanism.

Do you still see advantages, even with those special controls, to reclassifying as Class II for these devices, in terms of the innovation?

DR. SAPIRSTEIN: I do. As I said, there are a lot of -- the perception, which is not the only thing that we're talking about here, but the perception of what's required for a PMA does filter down, I think, on the innovation and what the manufacturers and sponsors would face. There's the ability, I think, with the special controls to really formulate them, perhaps, in a very device-specific fashion that perhaps might not take effect if it were a PMA. That's just my opinion.

And there is the obvious cost. I mean, PMAs are more expensive, PMA supplements are more expensive, and while it's not --

DR. B. ZUCKERMAN: Okay, we're not here to discuss economic costs.

DR. SAPIRSTEIN: Well, I was just going to say that, we're not discussing the cost, but that's another consideration, I suppose.

DR. B. ZUCKERMAN: Okay, let me take also a crack at answering your key question, Dr. Milan. You know, certainly the Agency as a core component is interested in improving its ability to be innovative and to do translational science. That's one of the key messages of Dr. Hamburg's recent perspectives piece, and it should really be understood. But by the same token, I think what we all need to understand is whether this device is

regulated as a Class II device or a Class III device, there are a core set of questions that need to be answered regarding the clinical trial, engineering, et cetera, and frankly the FDA would see innovation and decreased approval times in general being manifested by better interaction between a sponsor and FDA in terms of planning for what's needed. Secondly, the clinical trials generally are going to stay the same.

I do want to emphasize also that the development of a special control that's generally applicable can be a very time-consuming, difficult process. For example, one of the examples was the PTCA reclassification special control from Class III to Class II. Unfortunately, that took about 10 years to complete, and I think the Panel needs to reckon with the cost of having these data out there for a very important device technology.

DR. HIRSHFELD: Dr. Weisfeldt.

DR. WEISFELDT: I'd like to ask Dr. Quinn some questions about the recalls, if I could, because this is just editorializing just a little bit. I mean, I think the recalls are circumstances where the manufacturer is indicating something they have recognized and have some fear of in terms of legal action. So maybe it's a bit harder data than the death rates.

So would you review what a Class I and Class II recall are, I guess, as a starting point?

MR. QUINN: Sure. And also just to clarify, I'm not a doctor.

A Class I recall is a -- so all recalls, for the most part, recalls are

voluntary actions undertaken by the companies. We will call them up on occasion and suggest that they may have a recall situation and hope that they will take the appropriate action. Recalls, more often than not, also involve a violation of the regulations.

So the Class I recall, it's a violative product where there is a reasonable probability, reasonable, yes, a reasonable probability of serious adverse health consequences or death occurring from a malfunction related to the device. So Class I is most severe and is reasonable probability, Class II is in the middle with remote probability, and Class III is not likely to cause.

DR. WEISFELDT: So just extending that in a number of directions, the data you have for the number of recalls over time does not sort out Class I versus Class II. That's page 26, the bottom. It's the graph.

Do you have any information on the frequency of Class I recalls over time?

MR. QUINN: I don't.

DR. WEISFELDT: What about the issue of the type of device that has warranted a Class I recall? We, I think, learned that included in the database here is both AEDs on the wall and a much more sophisticated device with lots of stuff in it.

Is it possible that most of the Class I recalls were in those hospital-based devices with much more complicated electronics and the AEDs are relatively free?

MR. QUINN: I don't have a breakdown, but I do believe that we have Class I recalls for both segments of that population.

DR. WEISFELDT: The final question is, you said that six of the nine manufacturers had Class I recalls, which says that three of the nine did not. Can you tell us anything about the extent or the duration of use of those AEDs by those three manufacturers that did not have a recall? I mean, are there manufacturers that have been recall free and sold a lot on their license and had them out there?

MR. QUINN: Sure. The first point to that, the six of the nine manufacturers is within that bracket of 68 recalls which ended -- or started in January '05 and ended August of 2010. So as of today, I think that number has changed slightly. I mean, I don't believe it's nine of nine, but it may be seven of nine at this point.

I think there may be one manufacturer that, to my personal knowledge -- I might have to go back through and look at the spreadsheet, but I believe there's maybe one that does not have a recall, but I'm also not aware of the extent of their products they're actually manufacturing. As previously discussed, we have the AEDs and the accessories. And so if they're an accessory manufacturer, they may not necessarily have the Class I recall.

DR. WEISFELDT: Thank you.

DR. HIRSHFELD: All right, it's now 10:30, which is time for us to be scheduled to take a 15-minute break. I think we will be able to pick up at

10:45 exactly where we are now. So, David, I saw you over there. Thank you.

(Off the record.)

(On the record.)

DR. HIRSHFELD: All right, I'd like to reconvene now. And we basically have from now until noon allocated for the Panel to drill down more on the FDA's presentation this morning and to get clarification.

I'd just like to remind the members of the public who are here that this time is really not allocated for public discussion. That time is allocated this afternoon. So please don't expect to be a participant at this point.

So I would like us to start working on this by looking at the issue that was raised by Dr. Sapirstein this morning, about the degree to which there is an issue of the potential for stifling innovation in this field if these devices become regulated as Class III devices.

And I think there's two components to that. The first is, is this a mature technology in which there's relatively little opportunity for future innovation, or is there a lot of opportunity for future innovation? And, secondly, to what degree would the potential for innovation be stifled by being regulated as Class III?

So I'd like to have the Panel address that. David.

DR. NAFTEL: That's exactly what I wanted to talk about, so good.

DR. HIRSHFELD: Okay, I'll take my fee later.

(Laughter.)

DR. NAFTEL: So I'm a very young innovative guy who's been around for 61 years. I have worked with almost every heart valve company, several of the stent companies, I think, all of the VAD companies, and various other companies, and one thing -- and I shouldn't say this out loud, perhaps, where Bram might hear me, but every single company has said to me that we have a wonderful innovative product that FDA is slowing down the access and patients are not getting access to this soon enough and we've got the end-all and we know what we're doing. Every single heart valve company, VAD company, and several stent companies, they all say that, that FDA is slowing down innovation.

And, yet, all of these companies go through the PMA process and some of them get turned down because the results are not good and the innovation is not what the company thinks.

So I think my big question is, is an innovation discussion appropriate here in classifying a device, or is innovation more to what Bram said earlier, a few minutes ago, about perhaps refining and shortening the PMA process, but talk about the process and not the classification?

So I don't have a big conclusion other than to say that I'm unswayed by discussions of innovation in classifying devices.

DR. HIRSHFELD: Do other people have comments on this area?

Yes.

DR. LoGERFO: Well, maybe the deliberations here will guide some innovation. For example, one innovation would be that after one of these devices was used, you could interrogate it to find out exactly what happened.

DR. HIRSHFELD: Yes.

MR. BARRETT: I'm not going to directly comment on innovation, but I have a couple of questions for the FDA that I think are in the same domain as the two Panel members just brought up.

You know, one of the major components of a PMA submission is the submission of valid scientific evidence of a clinical study, and typically these studies are well controlled, prospective, and often randomized.

And, you know, if you've ever been on the writing end of one of these, it's a big part of what you have to prepare from a submission point of view. They're quite extensive, and I'm sure many of the Panel members have reviewed them. So even on the reviewing end of these submissions -- and that's a component of a PMA.

These Class III devices, the AEDs, have been regulated under the 510(k) regulation, and in the FDA Executive Summary, on page 7, it talks about different kinds of clinical evidence. And so this is really a two-part question for the FDA. It's not clear to me, of the X number of 510(k)'s that have come in for these devices, how many have been required to have the

clinical evidence that you might consider equivalent to a PMA. How many have had randomized studies, you know, well-controlled studies, prospective studies versus, let's say, human factors studies?

Because that's a big part of what you would be seeking if you moved from a 510(k) submission to a PMA submission, if it's true that some significant proportion of the 510(k)'s that come in don't require these more complicated clinical studies.

So in here it says, for example, the "FDA requests clinical studies for new defibrillation waveforms that are significantly different from existing waveforms."

My understanding of the regulations is, if a device is classified in Class II and it requires a 510(k), FDA at any time can receive any 510(k), look at it, claim that it's not substantially equivalent, in other words, it needs this new valid scientific evidence, and say that this particular device needs a different kind of evidence and needs a PMA. So you'll always have that authority to request that kind of submission.

DR. HIRSHFELD: Maybe FDA could help us with these comments and questions.

MR. SHEIN: Before we address that, if I could ask Oscar Tovar to come to the mike and address the question on the ability to interrogate what's stored in the devices, and then I will address Mr. Barrett's question.

DR. TOVAR: Yes. Currently, almost all the AEDs have the ability

to record information at the time when a shock is delivered. So it is possible to go back and look at the events that occur at the time that somebody delivered a shock. There are differences in how long or how much information a device can store. But most of them, the vast majority, record that type of information

I don't know if that answered your question.

DR. LoGERFO: Was that information used in the report that you showed earlier?

DR. TOVAR: For the MDRs?

DR. LoGERFO: Yes.

DR. TOVAR: No, we haven't -- right now, we don't analyze that type of information or we don't, as far as I know, have access to that type of information.

MR. QUINN: Brad Quinn. So when we do move into the realm of recalls and we are looking at multiple adverse events for these issues, we do on occasion receive information regarding error codes or problem device codes that are generated on malfunction.

And sometimes we're able to trend these and this information is then -- we can communicate back to the manufacturers and ask them, What does error code X mean? Do you have any current actions open for error code X? What is error code X leading you to? What could it be resulting from?

And we use all of this information as we move forward with a recall classification or building inspectional guidance that might go back out for an inspection. We do look into it and it is used in a compliance sense.

DR. LoGERFO: It doesn't seem to me to be the same, I guess, ideally, in my simplistic view of looking at this. The devices used on an airplane, the event is over, someone goes back to the device and there is a way to get some printout or some kind of hard copy to confirm the arrhythmia that was present and when the shock was delivered.

MR. SHEIN: Mitchell Shein. Many of these devices do have episode recording capabilities, and you'll be hearing from industry and have an opportunity to ask specific capabilities of them this afternoon. If you need to follow up on that now, we can continue down this path or you can ask the people who make these devices, who can speak to that directly.

DR. HIRSHFELD: Okay.

MR. SHEIN: Now, I'd like to get back, if I could, to Mr. Barrett's question, which was on clinical data.

The clinical trials that we would look for for these devices will be driven by the nature of the question or the change that's being made to the device. Currently, we frequently, if not always, get clinical data to some degree under the 510(k), and from my perspective in the branch, I'm not looking to see people come in with clinical data that is being provided just to do a clinical trial. It needs to address the question that's there, and I don't

think those questions will be different if this device is regulated under 510(k) or whether the device is regulated under PMAs.

So the clinical trial that needs to be done is going to be the same, regardless. What might be different is how the analysis at the end of the day is done. Is it a question of substantial equivalence, or is it a question of safety and effectiveness? And that's still going to need to be addressed, regardless.

So it's kind of -- it's a twist to your question. It's not do we get clinical data in the PMA and not get it in 510(k)? We already are getting under 510(k), and we would foresee continuing to receive appropriate clinical data when the need arises under the 510(k) paradigm.

MR. BARRETT: So if you don't mind just continuing this a little bit, there are all different kinds of studies, both in the design and complexity and on the follow-up, whether they're randomized, how much adjudication occurs, how much statistical analysis is conducted. And certainly there would have to be some differences in a relative level of expectation if it's a Class III and it has a PMA or if it's a Class III and it has a 510(k).

I guess what I'm hearing you say is you believe that if this Class III device stayed in Class III and required a PMA instead of a 510(k), that the kinds of evidence that you'd be looking for would not change. It would essentially be the same as you've been receiving. It would answer the same kinds of questions. And so you'd be looking for the same kinds of evidence?

MR. SHEIN: Again, if a manufacturer is making a change, for example, to the waveform, somebody comes out with a new triphasic waveform or whatever, then they're going to need to do a full-blown clinical trial to show that it's got reasonable effectiveness in converting an arrhythmia.

I don't think that the scientific rigor with which a clinical study is conducted should be any different whether that data is going to be presented in a 510(k) or whether it's going to be presented in a PMA. What may be different is, are you trying to establish is the device safe and effective, providing reasonable assurance of safety and effectiveness, which is the litmus test under PMA, or are you trying to use that data to show that you have a reasonable likelihood of cardioverting that patient and resuming their normal rhythm under 510(k) and therefore it's substantially equivalent to other devices?

So, again, if it's a simpler question, it may not need a full-blown or a large clinical trial. It might be a smaller demonstration trial. But the rigor in the data, I would hope, the scientific rigor would be the same, regardless. We want good, solid scientific data upon which to make our decisions.

MR. BARRETT: So III wouldn't be an arbitrary sort of upping of expectation because it's in a PMA?

MR. SHEIN: No. I think the only time you would up the

expectation is in the scope of the trial, and that should be to address the specific question that's being addressed in that trial. And that would be done in concert and development between the Agency and the individual firm.

MR. BARRETT: You may not be able to disclose this, and I just don't know this field well, but can you give me even a rough idea, was it zero percent that required randomized clinical studies, 10 percent, 100 percent, 50 percent? Just what kind of data are you typically -- have you historically required to determine substantial equivalence?

MR. SHEIN: Oscar, could you speak to the question of what we typically see from the firms in the 510(k) applications we currently receive?

DR. TOVAR: Yes. I would like to understand the question. Are you asking how many applications we have that --

MR. BARRETT: No, I'm really working out of ignorance here, and I'm just wondering, well, jeez, if you guys have gotten -- I'll make up numbers -- 100 of these things and 90 percent of them have a simple human factor study and 10 percent of them have had, you know, 50 patients in a single-arm study followed for a month, and then we go into the PMA world and there's an expectation that there would be, you know, randomized, controlled trials, it's really going to change the field. It's going to change what it takes to approve new devices. And I'm just working from ignorance and wondering what's submitted now and what might happen.

DR. TOVAR: Right, yes. For example, now the number of

applications that we have that include clinical data is low. We review very few applications which include -- that needs clinical data for the clearance of these devices. But, again, as Mr. Shein said, the clinical studies won't change whether we are in a 510(k) or a PMA because already, for example, with the new defibrillation waveforms, I put that as an example of a clinical study in which we have very well-established parameters for reviewing. We know the endpoints. We have a good idea of the sample size and the parameters that we need to review. And that could be reviewed under a 510(k) or a PMA.

But even now, for example, if we are in a 510(k) and we receive a new device that raises new questions of safety and effectiveness, that device would have to be reviewed under a PMA, and we have examples of that.

MR. BARRETT: I just want to make sure I heard you correctly. You said that very few of the 510(k)'s submitted historically have required clinical data, right?

DR. TOVAR: Yes, we review few applications that require clinical data at this time.

MR. BARRETT: So if we went to PMA, we would just exempt the clinical data or use literature?

MR. SHEIN: If I could address that. I think that for a new device that's coming out, we would expect an original PMA, perhaps, and then you have to do a clinical trial around that. Frequently, the applications

that come in now under a 510(k), as well as under PMA -- or not necessarily PMAs, I should say PMA supplements where they made minor modifications. They've got a change to the capacitors, they've got a change to an IC circuit or something that could impact safety and effectiveness. So in the 510(k) paradigm, it would require a new 510(k). The PMA would require a PMA supplement because it's a significant change. Those don't always necessarily require a clinical trial when they come through.

For large changes that could impact the fundamental therapy or the concept of the device, those are when we would start to look at things that would require all clinical data necessary. A change in the waveform is a prime example in this field. But that's not necessarily the case.

But under PMA supplements, every time they come in with a change, it doesn't mean they're going to have to come in with clinical data with that unit as modified. We wouldn't expect that. We would step back from that. But when they are making significant changes that can impact the delivery of the therapy or the ability in these devices to sense and detect and respond, then we need to make sure that we think very hard about whether clinical data are appropriate to reestablish that for the modified device.

MR. BARRETT: So I thank the Chair for his patience.

I have just one last point. Was my earlier statement correct? Is it true that if you or the Agency determined that these devices could be appropriately classified in Class II with special controls and you saw

something new, where you believed it wasn't substantially equivalent and maybe you needed that valid scientific evidence, a randomized control trial, you have the authority to go back to the sponsor and say, No, this isn't Class II, this is Class III; is that correct?

MR. SHEIN: That would be correct. At that point, if we were to make a determination of not substantially equivalent, then that would remand that device into Class III as a result.

MR. BARRETT: Thank you for your patience.

DR. HIRSHFELD: While we're on this theme, maybe you could clarify for the Panel exactly what would be required of the manufacturers of currently marketed devices. If the classification were to officially go to Class III, what would the manufacturers of currently marketed devices be required to perform and submit in order to maintain those devices on the market?

MR. SHEIN: Before I speak to the contents of the submission, I'd like to ask Margie Shulman to come up and address the process of when devices are called for a PMA, if she could.

MS. SHULMAN: Marjorie Shulman. Basically, if we do call for PMAs, there will be a proposed regulation that goes out and that will inform the industry, it'll appear in the Federal Register, and people will be given a certain amount of time -- sometimes it's a year, sometimes it's 18 months -- to prepare the PMA and have it submitted to us.

At that time, if they have a PMA that's in-house and it's fileable, so it has the basic information we need for a PMA, they're allowed to stay on the market. Companies that do not have that will then be taken off the market.

DR. HIRSHFELD: Okay. Well, what I was specifically asking was, does this, the requirements for this submission, do they differ from the requirements from a de novo submission of a device that's not currently marketed? A new company enters the field and says, We have a device and that device has never been marketed. Here are devices that have been in the field for a decade.

And so what are those manufacturers required to submit in order to maintain their marketing approval?

MR. SHEIN: I believe that the expectation is, is that they will fulfill and fill out a PMA as would anybody for a new PMA. That would have to include data that established that that device was safe and effective, likely to include clinical data.

Does that mean they would have to go back and do a de novo new study to establish that device? Not necessarily. But they do need to provide us with valid scientific data upon which a determination of safety and effectiveness could be made.

MS. SHULMAN: And this is Marjorie. A clarification. If a file is found not substantially equivalent for lack of a predicate or a new question of

safety and effectiveness, a company may come in with the de novo application, which is the automatic Class III designation. That is actually a classification of the device, and we would get any information that we need to classify that device and if we could place it into I or II. If we cannot write the special controls or it's just subject to general controls, the de novo application would be denied, and they would be required to submit a PMA.

DR. B. ZUCKERMAN: Okay. So let's put this in a practical -- a little bit more practical clinical context because that's an excellent question, John. And, in fact, I'd like to throw your excellent question back to the Panel because, regardless of the Panel's recommendation today, whether it's Class II or Class III, I think, from the Agency's viewpoint, there's a problem here. The problem is manifested by an unusual number of recalls, manufacturing problems and MDR reports, even though the data are limited.

So, you know, our first goal if we did go the PMA route would be to use our standard practices, which are least burdensome regulation and figure out what we have in our original clearance documents and see what needs to be supplemented. But that's going to be the case even if we go down a Class II pathway because we just don't have the assurance that we need right now for a very important device category.

So I hope that the Panel can help us to balance this innovation concept versus being judicious in our need for scientific data.

DR. HIRSHFELD: Okay. Does the Panel have comments? Yeah,

Dr. Slotwiner. Sorry, Magnus.

DR. OHMAN: So this is a very intriguing discussion because there are some similarities and there's some small differences in how we go about this, and I'm intrigued by the fact that, in the premarket approval or the PMA, there's an annual reporting system and currently none of the -- as I understand it, but please correct if I'm wrong. This is a jungle out there and it's hard for me to understand -- that doesn't appear to be the case, as it is right now. It's only as problems arise or as reports are coming in.

So my question would be, in a situation where you have annual reporting, can the FDA, or whoever is the most appropriate person, sort of tell me what added benefit is that annual reporting ?

And I'll have a follow-up question, depending on what the answer is.

MR. SHEIN: Well, currently we get annual reports in the PMA for the implantable versions of these devices. Annual reports come in to a PMA, and it's model specific. So it would be a little difficult to implement annual reports under the 510(k) paradigm because frequently model numbers stay the same but they may have subsequent 510(k) numbers. So which application do you report back to? So there's the matter of figuring it out and bending it where it's appropriate so you could locate it.

As to the information it provides, it provides some denominator information about number of units sold. It provides information

in some sense of -- one of the elements is to provide a bibliography of published reports on the continued field performance of the devices. And it gives us an opportunity to see a lot of field performance of these systems, once they're commercially available, that we wouldn't have prior to making the decision for approval or not.

And where appropriate, we might refer those things to compliance or to MDR to ask them to look further into that to see if there are trends or information that we do need to act on. So that's one of the things that annual reports provide.

DR. OHMAN: And so if I can lead on. So I'm humble, as a clinician, that many of the rare events are hard to ascertain. But we've been pretty good as clinicians to pick up rare events like lead fractures, stent thrombosis. But that's all been among the medical field, and the challenge, as I suppose I see it here, is that we're now asking the lay people or the manufacturer to do that in a non-cohesive manner. Am I correct with that?

In other words, we're relying upon a layperson that sort of says, you know what, that device didn't work as proposed, and then reports it in and that gets reported on. Is that an important distinction?

MR. SHEIN: Well, certainly for the publicly available devices, where there might be lay people working. If there's not an expert on site at the time it's being used, it would be hard for them to speak to whether there was a problem with it.

But as far as the companies, the companies provide the annual reports. MDRs come in under a different system. Those are typically provided by the manufacturer, but there are also user facility reporting, as you all well know and I'm sure that you faithfully report it when you see things. The information that comes in, just the same, is often dependent upon what's provided to the company for them to investigate and then provide it to us.

So you heard earlier that frequently we see MDR reports that are very limited in their content and information to act on. These are used primarily by us to develop signals. Are there things that we should be looking harder at and quicker at?

There's certainly been examples over the last many years. You mentioned the lead fractures and some of the other issues in the implantable leads, where the clinical community has picked up on these things a little quicker and been quicker to publish them. It's not that we haven't been following them, but our ability to take action -- I mean, when we take a regulatory action, it's on a broad, broad population.

Frequently, the things that are raised through the literature are often small series studies. Sometimes they're large, but they're often small, single-center, if not just case studies. But that gets the word out for people to be sensitive to them, and certainly as these issues evolve, people become sensitive to that. So I would hope that that would happen for the external

devices.

DR. B. ZUCKERMAN: So if we were to summarize, Dr. Ohman, the annual reports are taken very seriously by FDA because they definitely add a layer of value added upon the MDR reporting system. It's not passive reporting. There's a lot of useful information in it where we can pick up signals.

And, frankly, often when manufacturers have made changes that are not consistent with our regulations, this is the first pathway where we can get a handle on something that isn't right and it gives us an important signal here.

MS. SHULMAN: Marjorie Shulman. I just wanted to clarify one thing. Annual reports came up before and it was asked, could it be under a special control under 510(k)? There is that catchall phrase, any other information. But so far, annual reports have never been a requirement, a special control under premarket notification, and it would be more difficult because every new 510(k), every change would be a new number to submit an annual report.

But an annual report is definitely a requirement in the regulations under PMA, under 21 C.F.R. 814.84, and they do require the PMA holder to abide by a number of regulations that should be included in the annual report. And like Dr. Zuckerman said, the changes -- identify any changes pursuant to the device and report some of the scientific literature

concerning the device and any information known or that reasonably should be known to the applicant.

So I just wanted to close the loop on that, that an annual report is a PMA requirement and so far has never been a 510(k) or a special control.

DR. HIRSHFELD: Dr. Slotwiner and then Dr. Page.

DR. SLOTWINER: Thank you. In answer to, Dr. Hirshfeld, your question of balancing innovation with regulation, for this particular topic, I do think that the technology has reached some maturity level, although I'm sure that there are many innovations to come. But I think my concern as a clinician is more on the postmarket end.

And looking back at the FDA Slide Number 10, postmarket comparisons for 510(k) and PMA, versus the slide before it, premarket comparisons for a 510(k) and PMA, I'm more concerned that a device may -- I'm not concerned that a device won't come to market, but I'm concerned that a problem won't be picked up, won't be reported. And so I think that that is -- you know, that's a very major consideration for me as I look at these.

DR. PAGE: In response to Dr. Zuckerman's comment to the Panel, I think you framed it nicely in that you're not asking us whether there's a problem; you're telling us you see a problem and you're asking us how to improve or address that problem. Is that correct, Bram?

DR. B. ZUCKERMAN: Correct.

DR. PAGE: And I agree. I think there's pre and postmarket

issues here, and I don't think we can come to a conclusion, at least I personally can't, whether that's better under a Class III or a Class II 510(k) that has a whole bunch of other requirements. But one way or another, we need new requirements for this because, I agree, there is a problem.

Now, to answer Dr. Hirshfeld's charge to the Committee as we opened the session, and in complete agreement with Dr. Slotwiner, with regard to this device, I'm never going to -- I'm not going to call it fully mature, but it's come an awfully long way, and actually 10 years ago it was a pretty darn good device. And I am personally less concerned about innovation than implementation.

And this afternoon, I look forward to hearing comments, and I've already reviewed some of the letters that have been submitted with a desire and a zeal for better implementation of public access defibrillation. And I completely agree with that.

As a matter of fact, if we look around this room and I ask you where the AED is, there isn't one, I was informed. This is a great hotel and it's not unlike many others, but there is no AED in this hotel. So if any of us -- unless someone brought one with them today, you're better off in the airplane than you are here if you have cardiac arrest. Now, there are fire extinguishers, and everybody knows where those are.

So I'm coming at this from a strong desire to have better implementation of public access defibrillation, but I think part of that's going

to be an increase in trust in the effectiveness and safety of the device, which I think we're addressing today in terms of FDA's raising what I think is a good question: How do we address a genuine problem with some of these devices? Although most of them work perfectly, they're not where they could be.

DR. JEEVANANDAM: John?

DR. HIRSHFELD: Yes, Val.

DR. JEEVANANDAM: I think there's two components here. One is, is this going to work to defibrillate somebody? And the bigger component is, it's been laying on the wall for a year or two years and then it needs to be used now. Is it going to work then? Because if it doesn't work then, you have a catastrophic problem.

And I think, you know, when you look at self-testing, let's say it self-tests and it says the batteries are low. Well, then, is there a system in place? Does somebody go in and change it? It'd be great if they could wirelessly send an e-mail to somebody, saying my batteries are low. Come change me or change the device.

And the other problem that you have is that I think more and more of these are now being sold over the counter. So you can go to certain catalogs and buy AEDs, and how do you ever control those? I mean, there may be AEDs in people's homes. They don't have a technician to go in and check them on an ongoing basis. So yes, your AED may be in the hotel, but

has somebody checked it to make sure it works?

And, you know, if you talk about innovation, I think the real innovation would be to have some kind of communication protocol so, if there's a problem, somebody knows about it.

And if an annual reporting mechanism means that there's much better control or a much better reporting mechanism for all of these AEDs that are freely available now, I think that would be a very important consideration.

DR. HIRSHFELD: Good. Well, I think this has been a good segue into the next phase of this.

Mr. Dubbs, did you have a comment you wanted to make before we -- I'd like to shift gears a little bit, but --

MR. DUBBS: Well, on the innovation aspects, I think that, in many respects, not just this industry but many industries where you have your regulations, the industry manufacturers oftentimes talk about over-regulation and stifling of innovation. And I think it would be interesting to hear from the manufacturers this afternoon, if it's an appropriate question, to give us examples of where the over-regulation has stymied their efforts or if they know of other companies where it has created some sort of an impediment to moving forward with the technology.

DR. HIRSHFELD: Good, thank you. Okay. Now, I think what I'd like to have the Panel focus on -- we've got a little over 30 minutes before the

noon break. FDA has expressed concern that there is a product quality issue, and they are proposing that if they had Class III regulatory authority, that that would successfully -- or enable them to more successfully address this. So I'd like to hear the Panel's thoughts about the data that we have heard so far today that bears on the product quality issue and their thoughts about this aspect of things. Yes.

DR. LoGERFO: The item that caught my eye most this morning was the report on device evaluation -- and I need to understand this more clearly -- where two-thirds of the reports did not have a manufacturer evaluation. What exactly does that mean and what would be our goal in that regard? Because I agree with what was said earlier, that this is an issue of implementation. You know, the device has a lot of potential, but it's a safety issue after it's sold.

DR. HIRSHFELD: Okay, Mr. Quinn? Or who's going to respond?

MR. RALSTON: Luke Ralston, Office of Surveillance and Biometrics. And I believe the slide that you were referring to --

DR. B. ZUCKERMAN: It's 44, Luke.

MR. RALSTON: Forty-four.

DR. B. ZUCKERMAN: Page 22.

MR. RALSTON: Right. So that is based on our MDR search. And then I would like to go back to the second bullet on Slide 44, which is the possible confounding factors to that, which is that a number of the devices

are never returned to the manufacturer, which means that for some reason the clinical engineers or somebody in the hospital determines that it can be fixed there and the manufacturer decides that it's probably best to report the event. But if they never get the device back, then they can't evaluate it.

The second confounding factor would be the use of initial reports and follow-up reports because it takes some time to get the device back from the field and then complete a full analysis. And so there's always the possibility that reports come in in the future. And that was part of our analysis, was the initial reports versus the follow-up reports.

And just to give you the numbers that we have for that is that of the 25,658 initial reports with total results codes, those without an evaluation code have 17,608 with no result code. Of the follow-up reports, we had a total of 1,934, but those without an evaluation code was 11.

So it seems to indicate that when they do follow up and get the information in the future, it's complete and we get an idea of what the failure mechanisms are. And in the context of an annual report, going back once a year and giving us that follow-up information would be extremely valuable to us in determining a whole number of rates and other ancillary data that's concerned with basically how these devices operate in the real world.

So did that answer your question?

DR. LoGERFO: Yeah. One additional concern there is that -- and I don't know if this is correct or not, but it's a proposition -- that the

devices that are used on airplanes or in hospitals, if something fails, is it more likely that the manufacturer is going to get that device back and a detailed report?

And those devices would be used under the best of circumstances. So that's why that becomes a question. What are we looking at here when we look at the completed reports? Are these the more sophisticated devices in the hands of more sophisticated personnel, rather than those that are sold over the counter and used elsewhere?

MR. RALSTON: First of all, I think that would be a great question to also ask of industry. But based on my personal experience of the reports that I read, I'm much more likely to get a complete follow-up from the in-hospital, clinical-use devices because they have resources like clinical engineers and risk analysis people whose entire job is to follow up on those reports. And each airline may have, you know, different SOPs as to how to handle an event such as that. But I would encourage you also to maybe follow up with the manufacturers. They may have more details on that.

DR. HIRSHFELD: Dr. Naftel.

DR. NAFTEL: Just one thing I wanted to make sure I understand because with MDRs the user facility is supposed to submit an MDR and then the manufacturer is supposed to. So I just need to better understand. I think you said early on that everything we're talking about are the MDRs from industry and not from the user facility, or are we seeing a mish-mash?

MR. RALSTON: Well, the only people who are required to submit an MDR are the manufacturers, according to regulation. Now, we do also receive voluntary reports, but those are a very small, small fraction of the total number of reports that we receive.

DR. NAFTEL: Oh, I'm sorry. Since I spend a lot of my life filling out these MDRs, are you telling me I don't have to do them? Because I thought it was not voluntary by the user facility.

MR. RALSTON: Well, when we receive the MDR, it comes from the manufacturer.

DR. NAFTEL: Well, see, I'm positive I'm right about this, that the user facility is supposed to fill it out, and industry, and you've got to be careful when you -- I'm pretty sure I'm correct about this.

MS. SULLIVAN: It depends on the type of event. Death reports. User facilities are required to report injuries. They can tell the manufacturer, who submits a report.

I also should mention, when we talk about reports, we're not talking about events and we're not talking about devices. It's reports. And it is possible to get more than one report for the same adverse event.

DR. NAFTEL: And that's actually your goal, isn't it, for the user facility and industry? I thought you were hoping that it's 50/50 or actually you have two reports per event.

MS. SULLIVAN: Yeah, it varies by the type of device. Yeah, for

these devices, it's about 98 percent of the reports in the database during this time period where the source was the manufacturer. It's two percent for user facilities. Voluntary MedWatches.

DR. NAFTEL: Okay.

MS. SULLIVAN: You know, it varies depending on what the device is and who's using it. But you're right, there are some mandatory regulations for user facilities to report deaths.

DR. HIRSHFELD: Yes.

MR. BARRETT: A really quick question. You said you felt that the use of a PMA and a report might increase the quantity or the quality of this kind of reporting data.

If the information just isn't available to the manufacturer for whatever reason, what makes you think that moving from the MDR to the PMA and a report will provide either more quantity or quality information?

MR. SHEIN: Those are separate reporting systems. The MDRs would still be expected to be filed. The annual reports that we get would include a compilation and a summary of the MDRs that have been submitted for the reporting period. But the two are not exclusive. You wouldn't get reports in one and not in the other. MDR is a requirement that they would still have to satisfy.

MR. BARRETT: But if the manufacturer never knows, they won't know. They won't know in the MDR and they won't know in the annual

report, right? There's no information available, it's not available, regardless of the reporting mechanism, right?

MR. RALSTON: Right, that is true. And the requirement for an annual report, I think, would be the most useful for two reasons. One is the trend analysis that the company may be following on any given item or any given issue that they would then have to give us on an annual basis. And the second is just the statistics on the complete information that we get on follow-up reports, as opposed to the completed information that we get on initial reports.

MR. BARRETT: Isn't there a requirement under the quality system regulation that complaints are trended anyways, regardless of class of device?

MR. SHEIN: Could you repeat the question, please?

MR. BARRETT: Maybe I'm wrong, but I thought that there was a requirement that complaints be trended, regardless of class device, under the quality system regulation, under the complaint section.

MR. QUINN: Correct. So there is a section in the quality system that does involve complaint handling. And so the companies and manufacturers are required to assess complaints, and there's a definition for what a complaint is, what they're hearing, all sorts of stuff. That's going into complaint handling. They're going to make an adjudication on those complaints. That complaint could feed into the CAPA process -- you launch

an investigation, which should hopefully help find out those missing pieces of information that often come up in some of these events.

MR. BARRETT: So that requirement already exists for AEDs today?

MR. QUINN: Correct, it's part of the quality system.

DR. HIRSHFELD: Yes, Dr. Ohman.

DR. OHMAN: I'm trying to reconcile two things here. When we talked about the device failure and there was, you know, in 2010, maybe 7,000 of them and the vast majority -- this is on page 19 -- the vast majority were sort of automated, i.e., the battery had run out and so on and so forth, which picked up automatically.

And then I go to the next, which is basically we look at -- the second most common is power up, which basically, I suspect, but this is where I need the clarification -- this is on page 21 -- is that somebody figured out, or automatically, somehow, that the device was not going to work, and it raises for me the question, if it hadn't been checked or if the system hadn't been there, the device would've failed. But we wouldn't have reported it as a failure of the device necessarily because it could have happened outside a hospital environment where the failure of the device may not have been picked up, mainly because a layperson would have said, well, the patient was doing so poorly anyway.

So I'm trying to reconcile these because this gets to me. Does a

brake work in a car? Do they work really well when you really want them? And power up, to me, seems for these devices to be absolutely essential. It would be hard to figure out how the device could actually be out there not powering up adequately.

MR. SHEIN: I think you point to some of the problems associated with the passive reporting system, that we don't go out and actively collect that information addressing the numbers and who chooses to submit and when they choose to submit. We would hope everybody would faithfully submit, but we know that that's probably not the case.

As far as the individual diagnosis of the device, I should say, you have to get it in to understand what's going on with it. Sometimes they have a code. But, you know, again, if a device is sitting on the wall and it's got an error code in it, that this is not -- I'm not suitable for use right now, but you don't utilize it, is that an event per se? No, but I think it's a failure of the device that could've led to that.

It's kind of like if you have an implanted defibrillator and it has a fractured lead, but the patient dies before they ever need a shock and that never comes into play, is that a problem? I would offer that, you know, yes, it should've been detected. It could've been picked up and treated prophylactically, but it never became clinically relevant because the shock was never tried to be delivered.

So it's analogous in that sense in that we do need to know

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about these devices that aren't suitable for use at the time they would be called on, and the self-diagnostics are a significant tool in helping us determine that.

DR. OHMAN: And would an annual reporting system actually get to this problem?

MR. SHEIN: Annual reporting. Again, these are situations that we believe require MDR reports about, and we do get those reports, as Robbie and Luke have described. I think that the annual report would help to provide some analysis of those, some cogent analyses of the year that's elapsed in that period. That would give you an idea of whether there were trends that need to be acted on, as opposed to seeing some, you know, reports that come in periodically.

I want to get back maybe to what Mr. Dubbs was speaking about, or Mr. Barrett -- I forget who mentioned it to the right -- about annual reporting and MDRs.

There is alternative reporting for MDRs. They can come in. And the implantable device manufacturers do come in with periodic reporting. So they submit their MDRs in lump sum on a quarterly basis. The annual report is a PMA perspective of looking back on what's gone on in that device for the past year. But the individual reports would be summarized there. We would not expect them to re-provide the MDR reports that were provided through the course of the year, again, in the annual report. It's not

a duplicative report. We can't require that, in fact.

DR. HIRSHFELD: Yes, Dr. Lange.

DR. LANGE: Just to get back to what needs to be done to monitor and correct the situation, a couple points have been made. One is with reporting to MDR without knowing what the denominator is, without knowing what the actual MDR is, without knowing whether it contributed to the death or the guy just would've died anyway, in other words, detected asystole and didn't discharge appropriately.

So my question to the FDA is, would annual reporting, standardized annual reporting, correct the situation and avoid a PMA, that is, a classification as Class III and a needed PMA?

MR. SHEIN: I think that the way we've laid things out this morning, what the PMA process provides is a regulatory paradigm that already includes some of the elements that we believe are necessary, including the preapproval inspection, the annual reporting, the reporting of changes on an annual basis that might not require an application otherwise.

I don't know that it will correct all the numerator and denominator information. I don't know that it can. Because when you start talking about that, is it the number of devices that are out in the field or is it the number of devices in the field that are actually used?

So, again, those are some of the vagaries that go into the regulatory science that we all practice. But I don't know that the annual

reports can -- I can't tell you today that that would solve that problem.

DR. B. ZUCKERMAN: Right. So Dr. Lange, a great question. And at a minimum, FDA would submit that the problems cited on Slide 74 and 75, in toto, have to be addressed. It's not just one point that we believe needs to be addressed.

DR. HIRSHFELD: Okay. So I think there's a clear feeling that FDA would feel that this area would benefit from more comprehensive and more consistent device performance reporting than they're receiving currently. Is that a correct inference?

MR. SHEIN: I think that that's accurate. We would obviously prefer to see faithful reporting for all the devices, not just these.

DR. HIRSHFELD: And at some point we'll need to address whether the Class III versus 510(k) would facilitate that.

With the remaining time we have, I'd like to address the concern that was raised about product quality based on the existence of the MDRs and also based on the existence of the recalls. So I'd like the Panel to address and comment on the issue of whether or not there is an important product quality issue that currently exists.

Yeah, Dr. Kelly.

DR. KELLY: Well, it seems obvious, at least to me, that there is a product quality issue. But I think the biggest question I have is how much of that would be changed by having a PMA. Because since these numbers are

low, it seems like a lot of this is picked up after the device has been fairly widely disseminated.

So do we think the PMA, as opposed to Class II with special conditions, would change what we're facing now? Or is it more of a post-marketing problem?

MR. MacFARLAND: Good morning. My name is Bill MacFarland. I'm a Deputy Division Director in the Division of Cardiovascular Devices.

Yeah, I believe -- and we can let the Office of Compliance speak about what they actually do in a PMA review a little further. But many of these problems for which you've seen MDRs and recalls came after an FDA inspection. There's not a direct correlation there, but it happens.

And one thing on our mind as we reviewed this was, by having the up-front preapproval inspection that's already part of the PMA, that gives us a sense that we could really be more on top of evaluating quality up front before the product gets on the market. So we would hope to not see those MDRs and those recalls because we did the inspection up front.

DR. KELLY: But can you not do an inspection up front as part of a special condition with a Class II?

MR. MacFARLAND: So we do have the authority under Class II 510(k) to perform a pre-clearance inspection. Right now, if you look at all of the different 510(k)'s we did, it's just not routinely done. It is readily

evaluatable as part of the PMA program. For our whole manufacturing review under PMA, we do have guidance. So really it is feasible and it is technically possible under 510(k), but it's readily evaluatable under PMA.

DR. HIRSHFELD: Anybody else? Yes, Dr. --

DR. LoGERFO: Along that line and with regard to the inability to -- for example, a device not returned to a manufacturer. Now, in other industries, if there is a recall, repair of that device is facilitated. One of the reasons given here is that someone might not want to take away their defibrillator or have it out of action for a while, while it's being repaired.

So there are ways, I think, if you put the right things in place, that the industry could improve this by responding more aggressively to reports of malfunction.

MR. SHEIN: I think that that's perhaps a question best left for this afternoon when you can speak to the manufacturers on their perspective.

I think that, you know, to build on a little bit what Bill was suggesting about the special controls, I think if you look at all of the elements that we think are necessary to regulate these devices, we're not looking at those elements and saying that it should be 510(k) or PMA. I think if you look at all of the elements and then you look at total, what would you have to have in place in either one of those paradigms to make that happen?

I think when you look at all of the elements, we would have to

create special controls, we would have to create some special guidance under the 510(k) to get those things implemented. If you look at the PMA regulations as they currently exist, those things are already in place.

DR. HIRSHFELD: Yes, Dr. Slotwiner.

DR. SLOTWINER: When I think about the implantable defibrillators compared to these external devices, I think the performance charts that we have that we can use when we select which product we're going to use -- and those, I believe, are based upon the manufacturer following a small subset of devices prospectively. Is that something that could be considered under either the 510(k) or PMA, to request prospective monitoring of device functioning? A random sample.

MR. SHEIN: Are you referring to the product performance reports?

DR. SLOTWINER: Yes.

MR. SHEIN: I mean, those are developed and have been published by individual manufacturers at their discretion. They've laid them out to try to give people a better understanding of ongoing performance. Certainly some of the devices that are reported there are currently subject to post-approval studies, for which they base some of the data and pull some of the data in.

And yes, we would have the opportunity if it were appropriate to include either 522 studies, if we felt the need to call for those, or post-

approval studies that we would identify at the time of the approval, the PMA, for this class. But we would have to address a specific question with that. If you could help us develop what the question should be, that would be good insight for us to be able to utilize.

DR. HIRSHFELD: Yeah, Dr. Lange, did you have a question?

DR. LANGE: Yes. When I hear squealing in my car and I need to get the brake pads changed, I take it in and I say, I want to get the oil changed and the brake pads changed. And they say, listen, we have this thing where we can do everything because we have this plan B. We'll do that and change your windshield wipers and kick the tires. And I say, no, I just want these two things. That's really all I need. And they say, no, no, that's going to be special. We just have this thing that we do because this is the way we always do it and you'll get everything that you need, which is everything that I need plus some additional things, and at a time where I'm hearing where the FDA is trying to become faster and leaner and quicker about things, and I'm seeing these red flags about special concerns or considerations being outside the norm and setting a precedent and parallel regulations and where this could be a problem.

So what I'm going to do is -- it's a tough question, but I just, as the newest member of the Panel, would need to hear as to how tough it is and what problems does it create, and is it a precedent that we should start because it puts you in a direction, or is it a precedent that really puts you

behind a lot?

MR. SHEIN: I think that some of the concern is the time it would take to promulgate and get these in place, be it guidance documents or regulations. I think that, as Dr. Luke mentioned earlier this morning, that as -- if we were to build the special controls to include all of those elements, we really are getting very close to blurring the lines of distinction of what a Class II device and what a Class III device are and what it means to be regulated under 510(k) and what it means to be regulated under PMA.

I'm not saying that we're not willing to go there. I'm not saying that it couldn't be done. But I personally don't have any experience with that. We don't have extensive experience as a center in developing guidance or -- excuse me -- special controls of this ilk. And I can't tell you today what exactly it would take.

DR. LANGE: Thank you.

DR. HIRSHFELD: Okay, I think the final thing just before we wrap up for the noon break, I'm still not clear in my own mind whether the Panel is concerned that there is an important product quality problem out there, whether the data that FDA showed us today actually documents the existence of an important product quality problem or whether if there's a feeling that it's an artifact of the way the reporting system works.

So I'd like to hear from the Panel because I think this is a critical thing. If there is a product quality issue that could be addressed better by

regulation, then we need to decide that that exists or it doesn't exist. So I'd like to hear from Panel members about their feelings about that.

Yes, Dr. Karasik.

DR. KARASIK: Well, I think that's an excellent question because I'm having a very difficult time getting my head around these numbers. In the absence of a denominator, there is no way to know whether 28,000 MDRs is a big number or a little number. And I am equally concerned by the 4,000 number for defibrillators inside a hospital. I think that seems like a high number, too.

Some of us on this Panel have had a lot of experience with AEDs and doing clinical trials and may have an idea of how many devices are out there. Is it a million? Is it two million? This may be a very small number, depending on what the denominator actually is.

And I think, I am beginning to think, that it may be the only way we can actually get our heads around this number, is to impose some additional requirements on these manufacturers to provide this information, because I know the currently regulatory conditions, there is no obligation for them to let FDA know how many devices are out there and how many have been used and how many have failed, really.

So I don't know the answer to your question of whether or not this is truly a problem. All devices are manmade and all devices will fail, and I think we've learned that from our implantable defibrillator work. And I

certainly tell my patients that all devices are manmade and there may be a recall in your future and we'll deal with it. But I do think we have to understand that every company is going to be subject to some issue in the future, and what we have to do is try to protect our patients.

DR. B. ZUCKERMAN: Okay. So I think you've made some very important points, Dr. Karasik. We're dealing with limited data. But in addition to the MDRs, again -- and I think this is where you may want to talk more with Mr. MacFarland and Mr. Quinn -- Slides 51 and 52, on just the number of recalls, are from the FDA perspective, an extremely important signal.

This is a number that just outweighs, I believe, the number of ICD recall -- I'm glad you used that as an analogy -- and generally what we see in other important product classes, and I would like you to develop that with the FDA.

DR. KARASIK: Okay. So Dr. Zuckerman is telling me that this is an extraordinarily high number as compared to implantable defibrillators, and that's true. But how does this compare to other devices?

MR. QUINN: I'm glad you asked that. I got this number the other day. Out of the top 20 product codes for all devices, MKJ is number five. So out of all of them, they're number five according to a recent analysis.

DR. KARASIK: That's the total number of 68, not just the Class I recalls?

MR. QUINN: That's probably going to be more than 68. I think the analysis was done post this analysis that is part of the presentation. But out of all devices, they are number five for the recalls, and I believe it's between '03 and '09.

DR. KARASIK: You don't want to share with us what number one is, huh?

MR. QUINN: I can't remember. I just wrote down that they're number five. Sorry.

(Laughter.)

DR. HIRSHFELD: Yeah, Dr. Page.

DR. PAGE: Yeah, in answer to your question as to whether we see a problem, I see a problem here, and also I turn people's attention to Jignesh Shah and Bill Maisel's *JAMA* article from 2006, which was provided to the panelists, which I read with interest when it was published. And for those who don't know Bill Maisel, he chaired this Committee for a number of years. And this is a very compelling article, and the data that we've seen have shown that things haven't gotten better since this was published. So I think I would tend to agree that there is a problem that we need to address.

DR. B. ZUCKERMAN: Okay, I think that's another important point that you've pointed out, Dr. Maisel. I'm sorry, Dr. Page. Excuse me. Dr. Maisel's analysis was from about 1996 to 2006 and the problem just continues.

DR. HIRSHFELD: Other comments on this area? Yeah,  
Dr. Ohman.

DR. OHMAN: Yeah. Even we realize that this reporting system, the voluntary reporting system, is typically, at least when you come to pharmacological therapies, the tip of the iceberg. And I haven't heard anything that actually would tell me that what is being reported in this arena is substantially better than any other voluntary reporting system.

And if you go back, there's almost 1,000 deaths in the last five years, according to -- on page 19, the figure. And we can argue whether that's right or wrong, but if that's the tip of the iceberg, the number is probably higher. And if it's higher, it is a concern and we have to address it in such a way that we don't take away -- that these devices won't be available because that would be even worse.

But on the other hand, having a device that may not work is actually almost worse because the worst thing that can happen to us is that the public loses faith in a device that typically works. And that, to me, would be the ultimate disaster. Not that I think that's likely to happen. But ultimately we have to keep an eye on that.

DR. HIRSHFELD: Any other comments? Yes, Dr. Slotwiner.

DR. SLOTWINER: Just one thought about the numbers. I don't know if these are statistically significant because the reporting mechanism is so flawed. But thinking back to our experience with implantable devices,

when we are concerned that there may be a signal, we have learned that there is such a problem relying upon the responsible parties as the only source for the number.

You know, I don't know how to get around that conflict of interest, but hopefully we can stress the importance of the public reporting these problems because there's such a conflict of interest when it's the manufacturers alone. I just wanted to make that point.

DR. HIRSHFELD: Yes.

MR. SIMON: Could I just make a comment? If, as I understand, you're effectively dead with ventricular fibrillation and there's no device there, you're not coming back. If there's a device there, you might come back.

Do we have the actual number of people who die each year from ventricular fibrillation?

DR. HIRSHFELD: I think that number is quite well known. It's been in the articles published by several members of the Panel. They might want to enlighten us.

DR. WEISFELDT: The number of deaths per year in the United States is estimated at 300,000 a year, and the percentage from the most current data of the incidence of VT/VF is 23 percent of those patients. So the number of deaths per year from VT/VF, being the first recorded rhythm, VT/VF, is 23 percent of 300,000.

And if you then go to saying a lot of those people were really in arrest a long time, if we just limit our subset to bystander/witness duress, you'll see some data two days from now that shows that about 35 percent of those people who have observed arrests in a home have VT/VF. And in public locations, about 75 to 80 percent of those people who have observed arrest have VT/VF. So if you're lucky enough to be observed in a public place, a high incidence of VT/VF for an AED would be extremely beneficial. At home it's less beneficial.

DR. LANGE: So get out of the house.

(Laughter.)

DR. HIRSHFELD: Yes.

DR. WEISFELDT: Since I got the microphone, the data from the Maisel paper shows the sales of AEDs, I assume, in the United States and that it shows about a million by 2006, and if we assume no increase in sales over the last five years, which the graph suggests that that's probably an underestimate, you'd have to say it's two million. And if all of those have a self-check on them that says something's wrong in whatever thousands of them, you're talking about less than one percent incidence.

And the question is, you know, how many devices do we have of any type that are not going to fail one percent of the time? So that's why, in my own commentary, I'm more concerned about the recalls and the Class I recalls than I actually am about the event reports.

And in conversations over the break, people -- the FDA said that the actual number of recalls was seven, Class I was seven out of nine, and that the two manufacturers that did not have a Class I recall are people that have entered the market recently.

So I am really concerned, but my concern is based upon the Class I recalls.

DR. HIRSHFELD: Yes.

DR. LoGERFO: Just to follow up on the 300,000 people with cardiac arrest. And I thought I read somewhere, in preparing to come here, that the estimate was that if this device had been available, approximately 450 additional lives would've been saved. Did I read that correctly?

DR. WEISFELDT: The figure that you have is the estimate of the number of actual people today in the United States and Canada who are being saved by the AEDs. It's about 500 a year. This is an extrapolation from data on 21 million -- it is a network that covers 21 million people.

If you say how many people appeared in a multivariate analysis to be saved by virtue of the AED itself, it was 500 people per year in the United States and Canada.

DR. HIRSHFELD: I will just mention, our institution happens to be the first responder for Philadelphia International Airport, where there are AEDs very widely distributed, and I would say, anecdotally, we probably take care of 6 to 10 patients a year who were successfully defibrillated at

Philadelphia International Airport. And many of those people wind up having cardiac pathology that is eminently suitable for treatment and they get successful treatment and really put this otherwise catastrophic event behind them. So there's no question that for a few lucky people, these are really game-changing devices.

DR. LoGERFO: But in that situation, the Philadelphia Airport, there are very trained people available. There are almost always physicians around, nurses and defibrillators are everywhere, and I would bet there's an SOP where someone checks them out and makes sure they power up.

But what I'm concerned about is the broader use where those things aren't in place because if you call 911 you do get a defibrillator. It's just the time difference we're talking about. And is it better?

Then you would have to consider, if someone arrests at home, is it better that a neighbor runs over with their defibrillator kit and puts it on a patient, interrupts CR, by the way, or wait for 911 and the professionals to come and apply that same technology but in a professional way? That, to me, is a key difference in opening this up to the public. The airports, hospitals, and places like that, they're very different.

DR. PAGE: With all due respect, most resuscitations in airports are by lay people. And, for example, the 40 percent survival on aircraft was by flight attendants. Even in Seattle, which has the greatest resuscitation network in the world, in terms of time that it takes to get an ambulance

there, you're better off if you are defibrillated promptly by a bystander. And that's where it's really good, when you go to cities where their survival is less than five percent, like Chicago or New York. The key is public access defibrillation. And these devices are so simple to use.

There was even a trial in Seattle that demonstrated that if you took a paramedic and had them resuscitate a dummy, told to go into the room, a trained paramedic, they got that patient shocked within 62 seconds, I believe.

If you took a naive sixth grader -- now sixth graders are pretty slick with electronic devices. If you took a naive sixth grader with no training and just the box and go figure this out, it took them 90 seconds. And clearly time to defibrillation is key.

In casinos, for example, which again have a standard operating procedure, but these were security guards, those who were resuscitated within three minutes, 74 percent survived. So three out of four can survive cardiac arrest just compared with such low numbers.

So please don't get the impression that these devices are typically operated by professionals. They're best off being in the public, operated by people with minimal training, if any.

DR. LoGERFO: But they do have to power up.

DR. HIRSHFELD: Right, okay.

DR. PAGE: It needs to work.

DR. HIRSHFELD: Right, right. So I think everybody agrees that these are potentially valuable devices.

I think at this point we've reached the noon hour, so at this point we will break for lunch. And the Panel members are all enjoined not to discuss the meeting topic during lunch.

And we will reconvene in this room at one o'clock. The room will be secured while we're out, so please take any of your belongings with you, and you won't be allowed back in the room until one o'clock. So thank you.

(Whereupon, at 12:08 p.m. a lunch recess was taken.)

AFTERNOON SESSION

(1:04 p.m.)

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

And Mr. Swink will now read the Open Public Hearing disclosure process statement.

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

statement, it will not preclude you from speaking.

FDA has received three requests to speak prior to the final date published in the Federal Register and has chosen not to trigger the lottery. In order to allow all who request time prior to the deadline published in the FR to speak, we have allotted each speaker 20 minutes to present.

I also want to state, we did receive three other requests after the FR published date, so they will be given five minutes each, after the first three.

DR. HIRSHFELD: Okay, the first speaker is Paula Lank, who represents Physio-Control. Would you please come to the microphone? And we'd ask you to speak clearly so that the transcriptionist can provide an accurate transcription of your remarks.

MS. LANK: Good afternoon, representatives from the FDA, industry, the Panel Chair, and the Panel members. Thank you for the opportunity to present today at this important meeting.

I wanted to take just a brief moment to address a few other questions that were asked this morning, but not answered. One is do AED algorithms identify and treat atrial fibrillation? The answer is no. An AED algorithm makes one or two determinations, shock advised or no shock advised, for rapid ventricular tachycardia and ventricular fibrillation.

Secondly, all AED products and manual devices with AED capability store electronic device data in the product. It can be downloaded to a

computer. It can be looked at on the computer. It could be printed out and analyzed. And some of the best EMS systems in the world do this on a routine basis. And some of them also record voice at the scene and listen to the whole voice recording of the event.

The last question that came up, types of devices, LDD, those are products that are manual, a monitor/defibrillator without AED capability. Since 1992, Physio-Control has not produced a product like that. All of our devices have AED capability, either just AED capability or a combination of manual with AED as an optional mode to use.

What I'd like to cover today includes a summary of rationale that supports down-classification of AEDs into Class II, to talk a little more deeply about the FDA recommendations, the majority recommendation and the minority recommendation, and then touch on the plan of action for implementation of 510(k) changes recommended and published just last week by the FDA.

I think many in the audience, and certainly on the Panel, had an opportunity to review the summary report that FDA put out. I thought it was meaningful to review the minority recommendation, which states that "We anticipate that AEDs will continue to iterate and improve their technology in the future, so future regulation under the PMA regulations may be overly restrictive and may slow the pace of improved AED technology reaching the marketplace. Given the ubiquity with which AEDs are now present

throughout the U.S., slowing down the design and implementation of device iterations might then have an unintended negative effect on the public health.

"As an alternative to reconfirming the Class III status of AEDs, FDA could alternatively reclassify the devices to Class II status and require 510(k) clearance prior to market entry."

And importantly, "FDA could couple this reclassification to Class II with a strengthening of the 510(k) process" -- which we'll talk more about -- "with the establishment of appropriately chosen special controls," which are in the FDA 510(k) action plan.

"Finally, the classification of AEDS into Class II," as we've heard earlier today, "would not preclude FDA from requiring PMAs for new AEDs if select changes to AEDs raise questions of new intended uses or new types of safety/effectiveness questions."

Before I advance to the next slide, I want to make sure that the Panel in particular is aware of an initiative that FDA launched on November 15th at the American Heart Association scientific sessions. It's called the "External Defibrillator Improvement Initiative."

There are three broad objectives underneath this initiative. One is to partner with industry to advance innovation in the defibrillator industry, number two is to identify and address problems as quickly as possible with these devices, and number three is why we're here today,

which is to determine the appropriate regulatory path with which to regulate these products.

So AEDs do meet the statutory criteria for Class II classification. Existing data, including those reviewed by FDA today, demonstrate that AEDs are effectively used and with great benefit. They're associated with risks that can be appropriately controlled using the general controls in place and additional special controls.

Because there is sufficient information to establish special controls to provide a reasonable assurance of the safety and effectiveness of AEDs, they meet the definition of a Class II device and are appropriate for down-classification.

So FDA's Executive Summary looked at this information specifically: performance testing requirements, recalls over the past five years, medical device reports, and scientific literature. And I think the question posed before us today is do the results of the FDA analysis, as detailed in that report, support the recommendation, the majority recommendation?

So if you look specifically at performance testing requirements, all of these requirements are available today through special controls. In addition, there are more special controls that will be promulgated through guidance documents in the new proposed changes to the 510(k) process; in particular, the proposal to move these products under PMA that would be a

requirement to add PMA pivotal site biomedical or bioresearch monitoring.

We submit that these inspections are not warranted for the following two reasons. FDA can currently inspect clinical trials supporting a 510(k) where the specific circumstances warrant an inspection. However, available data do not support the adoption of BIMO audits as a routine matter; thus the special control is not warranted.

In addition, as you heard earlier, the number of randomized controlled trials that have been done on external defibrillators, whether they're AED or a manual AED, is very small, and when they are required, they're necessary for new technology; movement from the monophasic waveform to a monophasic waveform and the next one was pediatric defibrillation with an AED and being able to appropriately reduce the energy. In that case, it was done in a pediatric pig model, experimental model.

So let's look at the recalls over the past years, the past five years, and the medical device reports data represented in a summary presented earlier today.

So per FDA's data, the vast majority of recalls are associated with these two issues, purchasing controls and design controls, both of which, we submit, can be mitigated through the adoption of special controls, standards, and methodologies.

Now, these two areas, purchasing controls and design controls, represent 92 percent of the recalls reported by FDA. The other four to eight

percent were associated with manufacturing or a much smaller percentage allocated outside of these two primary areas. So based on that, FDA's recommendation to move to PMA for broad-scale manufacturing reviews is unnecessary and overly burdensome.

FDA, industry, and public health would best be served by using the current general and special controls for these two areas and the option for premarket approval inspections provided for in the proposed FDA 510(k) recommendations.

So let's turn our attention briefly now to medical device reports. The regulation defines that a reportable event -- an event must be reportable when the device malfunction has actually caused harm or has the likelihood to cause harm if the malfunction were to recur, so-called presumptive harm.

Each reportable event is given equal weight, no matter whether the malfunction was detected by the device and no patient impact occurred, or during therapy where there was a reported adverse event. The majority of malfunctions are detected prior to use on the patient. We heard earlier today from FDA that 90 percent of that large number of MDRs were identified by the device, the device was removed from service and appropriately addressed the issue.

In addition, we heard that the number of MDRs is increasing. The number of AEDs in use has grown rapidly over the last 10 years, from an

estimated number of about 100,000 to 1.5 million devices worldwide, and that number is growing. Thus, the number of reports is best considered in the context of a denominator. And I think there were several Panel members who brought that up. So given the growth in the AED installed base, it is reasonable to expect that the number of MDRs would correspondingly increase during this time period.

I've also listed just a few other reasons for the increased number of medical device reports. This is not an exhaustive list. But we find that often users, whether they're in the hospital or outside the hospital, use products beyond their useful life, their designed useful life, which gets into issues around electronic component reliability, and how do we address that?

Inadequate user maintenance. Devices in and of themselves don't save lives. Devices as a part of a well-developed system, whether it's in a hospital, in the EMS, or any commercial setting, requires people to be responsible for training and maintenance and assure the readiness of those devices on an ongoing basis.

FDA, industry, and public health would best be served by focusing efforts to analyze the existing MDR data to understand the actual contribution a device malfunction may have had on patient outcome.

One of the follow-on activities from the workshop held on December 15th and 16th was an interest, a strong interest on the part of FDA and industry, to collaborate, to look at the existing data and say, how can we

better analyze the data you already have? And then, secondly, based on that analysis, to perhaps collect some more meaningful data. Was it truly on a patient or not on a patient? Was it self-detected prior to use? If it was an adverse event, what was the likelihood that it actually did cause or contribute to patient death?

I think we heard earlier from FDA that it's somewhere around one percent of the adverse events where it was reported that there was a connection between a device malfunction and the patient's outcome.

Requiring Class III classification or PMA for review of AEDs is not necessary to achieve these analyses. FDA can implement special controls to require AED manufacturers to provide these types of information and analyses as needed.

A few words about the scientific literature. FDA did provide a bibliography of articles in their summary. They did not include an analysis of those articles, and I wanted to just highlight two, I think, well-known studies.

One has been mentioned today, the public access defibrillation trial published in 2004, which was the largest randomized, controlled trial evaluating and comparing two arms where layperson responders, volunteers were trained to use the AED and had to do CPR, or just trained in how to do CPR.

And I want to highlight this direct quote. "In public locations, where approximately 20 percent of out-of-hospital cardiac arrests occur,

implementing an organized emergency response plan and training and equipping volunteers to provide early defibrillation with an AED doubled the number of survivors to hospital discharge after out-of-hospital cardiac arrest."

The second trial just recently published by Dr. Weisfeldt, et al., as he mentioned, performed a population-based cohort study to address the effectiveness of contemporary AED use in a very large resuscitation outcomes population of 21 million being conducted in North America. In this study, the final outcome or result was that the application of an AED in communities was associated with nearly doubling of survival of out-of-hospital cardiac arrest, which reinforces the importance of strategically expanding community-based AED programs.

I think it's important to note that in both of these large studies where data was very carefully collected, put in a database and analyzed before reports or results are reported, that there were no reported risks or issues associated with the use of AEDs in either of these studies in the publications.

This is just a short list of the scientific literature. There's a large body of literature supporting the safe and effective use of these products.

So the alternate proposal based on the data presented in the FDA Executive Summary, and an analysis of that data, is that Physio-Control

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believes that general and special controls currently in place and the increased control provided by the proposed FDA-planned 510(k) recommendations, which are drafted and most of which are recommended to be completed this year, are sufficient to reasonably assure the safety and effectiveness of AEDs.

The annual reporting requirement that was discussed quite a bit this morning, I think if we don't address the limitations in the current MDR data, implementing an annual reporting requirement, which can actually already be done, is not going to be any better, the data won't be any better at the back end. Therefore, down-classification of these devices into Class II is the appropriate regulatory approach.

So here are just a few reasons, additional reasons, why not PMA: the unintended negative effect on public health, which was mentioned in the minority recommendation from FDA; there will be a delay, a substantial delay to getting products on the market.

The 510(k) process is typically a 90-day process if a company can respond to a request for information that the FDA has within a reasonable time frame, or that could stretch out. That time will at least double or triple under a PMA, and there isn't a requirement for how long it needs to take.

The cost. It's probable that the cost of these devices will increase as a result of this overly restrictive regulatory burden. It's also possible that the number of manufacturers who can actually enter the market

will be reduced. Access to these products will likely also be reduced. And potentially, the risk that we have an opportunity -- or the opportunity will be lost and fewer lives will be saved. And, overall, I think the data just really doesn't support broadly applying the PMA approach to these devices.

So why Class II with special controls? The proposed FDA 510(k) planned recommendations provide adequate and appropriate control and flexibility. They're supported by the data. This approach provides all the tools that FDA needs to appropriately regulate these devices. It provides the flexibility for FDA to just ask for what they need, when they need it, based on the submission. The timing and review process is less burdensome and more predictable than PMA and PMA supplements for Agency and for industry.

The Agency is already planning for resources needed to implement these recommendations. In fact, they started this process of analyzing the 510(k) process back in September of '09. There have been a number of public hearings. They published a 200-page report last August that included a lot more actions. They've now boiled that down, based on all the comment that they received, to an initial list of about 25 actions.

In addition, this approach does not require regulatory amendment. It's done through the issuance of guidance documents, which the FDA is very adept at doing. Innovation is not delayed and greater access to lifesaving devices can be provided.

Again, three summary points. The majority, 92 percent, of

recalls are attributed to purchasing controls and design controls. The proposed 510(k) planned recommendations provide an option for greater control in both of these key areas.

The current FDA data shows that 97 percent of MDRs are malfunctions, which in many cases -- and we heard today, 90 percent of the time -- are self-detected by the device or the user before it's used on the patient. And three percent of the time there was a reported adverse event. And we also heard that, of that three percent, a significant number by the reporter were indicated not to be associated with the device associated with the patient's outcome.

So the FDA-planned recommendations for the 510(k) includes tools that can be applied to assure the safety and effectiveness of AEDs where warranted by the data and support the appropriateness of regulating these devices under a Class II classification.

Thank you.

DR. HIRSHFELD: Thank you. Okay, we will now hear from Diana Zuckerman, who is representing the National Research Center for Women and Families and Cancer Prevention. And I assume, no relationship --

DR. D. ZUCKERMAN: No relationship.

DR. HIRSHFELD: -- to anybody at the table?

DR. D. ZUCKERMAN: Yes.

DR. B. ZUCKERMAN: That is correct, for the record.

MR. DUBBS: Are there some questions we can ask the representatives?

DR. HIRSHFELD: That will be afterwards. We'll have the presentations first and then the questions.

DR. D. ZUCKERMAN: Okay, thank you very much. And no relation, yes.

I'm Dr. Diana Zuckerman. I'm President of the National Research Center for Women and Families. We're a nonprofit, independent research center that focuses on improving the health and safety of men, women, and children by looking at research results and synthesizing and comparing different research to determine what are the strategies that work best, what are the treatments that work best, and what do we know and what don't we know to answer various medical and health-related questions.

I do not have any conflicts of interest. Our center does not receive or accept any money from medical device companies.

I should say that my own perspective is as someone trained in epidemiology at Yale Medical School. I was on the faculty at Vassar and at Yale and conducted research at Harvard. But I've been working in Washington for the last 25 years, where my focus has been on health policy. I've written numerous peer-reviewed articles and some book chapters having to do with medical devices and specific medical devices as well as policies related to medical devices.

As I think everyone here knows, and it was certainly in your FDA summary, almost 300,000 Americans collapse from sudden cardiac arrest every year, and to quote the FDA's summary, "Survival depends upon a rapid sequence of rescue events that includes a successful delivery of a shock from AEDs."

And I wanted to focus on a few of what I think are the key issues here. I'm not going to get very technical. I'm going to really talk about what is a Class III or a Class II device and what is intended in the law in terms of public policy and public health.

As the FDA has pointed out, rescuers have only minutes before these rhythms degenerate beyond rescue capabilities. In other words, people will die within minutes if these products don't work when they're there or if they're not there.

I think an important issue to get into briefly, at least, is how stringent is the PMA process? Clearly, it is more stringent than the 510(k) process, and that's what today is about. Do we want to go to a more stringent process?

But I also want to point out that although the PMA process is absolutely more stringent and has more safeguards than the 510(k) process, it is actually somewhat less stringent than the approval process for prescription drugs.

So, in this country, we have a process for prescription drugs

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that we've all accepted, and regardless of whether those prescription drugs are lifesaving or whether they're, you know, for temporary relief of pain or stomach upset or numerous other things that are not life-threatening, they are actually held to a higher standard in terms of requiring double-blind clinical trials, much larger samples and so on. I'm not saying we would want to test AEDs with double-blind clinical trials. I'm just saying that, in the grand scheme of things, what is being proposed is a reasonable increase in safeguards in testing.

So, really, the question before you today is should lifesaving AEDs be held to a higher standard than they have been, a higher standard than the 510(k), but one that is still lower than that for prescription medications that are not necessarily lifesaving? That's the only choice you have because there is no higher standard than the PMA for devices.

And in their own summary, the FDA has said if the device is of high risk, then the FDA review of AEDs "warrants the additional controls and rigor necessary to properly determine the safety and effectiveness of the device." And that is the PMA system. So the question is, is this a high-risk device? Because if it is, then it does warrant these additional controls.

I just want to say, I'll be publishing an article in a peer review journal shortly, that we studied the high-risk recalls. You already have some of the data that was provided to you, but I just want to say, our study looking at high-risk recalls, high risk as defined by the FDA as causing death or

permanent serious injuries, that the AEDs were responsible for an actual surprisingly large number of high-risk recalls over the last five years. And in, I think, any reasonable definition, a device that can result in a high-risk recall is a high-risk device.

This is just a summary of the high-risk recalls that we saw, looking from 2005 through 2009. I know the FDA's data went a little bit into 2010. I'm not going to go into each one, but you can just see that every few months there was another recall. These are many different companies and many different products. It isn't just one or two or three. But some of these products were recalled more than once. So they were recalled, some kind of fix was made, they were back on the market, they were recalled a year later, and so on.

GAO pointed out that the law requires Class III devices to be approved through the more stringent PMA process. So that's the law. And what GAO said, and FDA agrees, FDA needs to either start requiring PMA approval of AEDs, as the law requires, or they need to reclassify AEDs as Class II devices.

Class II devices by definition are a moderate risk, and I don't see how we could ever consider an AED, which can save a life or if it doesn't work, a person will die, I don't think we can consider that a moderate risk. I think that we have to consider it a high risk. So just looking at this in a logical way, it seems to me that AEDs can't be classified as Class II because they're

life-saving.

And the law is actually clear. PMAs are the proper pathway for review for Class III devices. And there's a reason for that. The law was set up that way for a reason. They wanted to make it easier to have low-risk and moderate-risk devices get on the market more quickly, but they wanted the most risky devices, the Class III devices, to have more stringent safeguards to protect patients and to protect the public health.

So we can get very complicated about special controls and using the 510(k) pathway and adding special controls. But every time you do that, you add a layer of complication and uncertainty. So although I understand that the companies would prefer to stick with the 510(k) process, which is easier for them, less expensive for them -- and by the way, the user fees that a company has to pay when they apply through a 510(k), usually the maximum is about four or five thousand dollars, where it can go up as high as a couple of hundred thousand dollars.

So there's a huge financial incentive not to do a PMA. But that doesn't mean that's good for the public health. And although I've heard that there are some concerns and I understand that there are some concerns about hurting the public health by slowing down innovation, the greater risk is to hurt public health by having products that are being used and available and bought and relied on that can't be relied on because they don't always work or they don't work correctly.

So really the simple issue is, is this product a high-risk device? If it is, you need to vote to recommend that it stay in the Class III where it is and go through PMA.

You've heard about Bill Maisel's research, and some of you know him. So, clearly, they found that more than 20 percent of the almost one million AEDs in circulation had been recalled by the FDA.

So we've heard a little bit about denominators. As researchers we have to care about denominators. But there's all kinds of denominators. In this case we're talking about one in five that were in circulation were recalled. That's a very high number.

I don't think we're ever going to find out what percentage of AEDs worked and saved a life versus those that did not work and therefore somebody died. I don't think we're going to have those numbers. But we do know that there are a lot of devices out there that had to be recalled because they could not be considered reliable and might not work.

This is just a slightly simplified version of FDA's own summary statistics. I just want to give a few illustrations.

We have the deaths, which total 721. Again, as you've heard, it's expected that that's the tip of the iceberg, even though the numbers aren't always reliable and some things may have been counted twice. But since almost all the reports came from the companies, that seems unlikely.

There are injuries, there are malfunctions. It's not always clear

what that means, and so I want to give just a couple of illustrations. And this is from the MAUDE database. This is from the FDA's website.

In October 8th, 2006, fire department personnel had repeated problems with the connect electrodes alarm and the LIFEPAK 500 was not successfully put to use until an ambulance crew arrived. And in that case, the patient's outcome was not known. So it wasn't working, it didn't work. No report was given about what happened to the patient. That was not counted as a death, but obviously, because of the time involved, very likely that person was harmed.

On December 10th, 2007, a patient was at the hospital for an outpatient appointment. So he was in the hospital, went to the cafeteria with his family, and he had a cardiac arrest in the cafeteria. Well, you know, if you have to have a cardiac arrest, presumably a hospital is a better place to have one. But in this case, the Zoll AED Plus powered up, went through the self-test, advised that the unit was okay, and then shut itself off, and this occurred two times according to the MAUDE report. So it was eight more minutes before a shock was finally produced, and the patient died.

I'm only using examples where there were well-trained personnel that knew how to use it. A whole other issue is whether there's adequate research to show that regular people in a stressful situation -- and that might be their spouse going into cardiac arrest -- will be able to use these devices. And I think that's research worth doing.

And my last example. On December 11th in 2008, a police officer attached an AED 10. The machine appeared to be working, but according to the police officer, it was "slow to charge." It failed to deliver even one shock. A manual defibrillator was brought to the scene, but in spite of eight shocks from that and drug therapy, the patient died because of the delay.

So I think that's a good illustration of the kinds of things that happen. I didn't bother to get photos of patients who died from AEDs that didn't work, but I think all of us in this room know at least one person who might benefit from an AED at some point in the future, and we sure would like that device to work.

The main argument against switching from a 510(k) to a PMA is that PMAs could slow down the process of improving AEDs. And yes, when you have a more stringent process with more safeguards, it can slow down the process. But we've been selling AEDs for many years without those concerns and without -- you know, without PMAs, and I do think the products have improved. And, yet, the recall percentages are still enormous, and the number of devices being recalled is still enormous. So, clearly, we haven't interfered with innovation, but we have paid the cost in terms of devices that don't work as well.

I just want to say that, as a public health person, you know, I'm all for innovation, but I care about innovation in terms of making products

better. I want those products to be safer. I want them to be more effective. Being new isn't enough. Being different isn't enough. We want them to be better.

The PMA safeguards are important because they can make sure the product works by adding rigor to the process, and that includes better clinical data, premarket inspection -- it's very important to have it inspected before they're sold -- as well as postmarket studies. But we don't want to put all of the safeguards at the end. We want the safeguards before the products are put on the market, not afterwards, not after people have been hurt.

And just to say quickly, we work with many experts in the field, from across the country, from academia, from other nonprofit organizations, and although I'm only speaking for myself today, there are many groups who share our concerns.

I also want to just mention noted cardiologist Dr. Rita Redberg, who's editor in chief of the *Archives of Internal Medicine*. She couldn't be here today, but I spoke with her yesterday, and she expressed her concern about the large number of high-risk cardiac devices that are getting on the market through the 510(k) process and therefore don't have the clinical data or premarket inspections that help ensure safety and effectiveness.

We share her concerns about harm to her patients from devices like the AEDs that have been cleared by this 510(k) pathway. And because of her concern for patient safety, she opposes the continued

clearance of AEDs via the 510(k) process.

And with Dr. Redberg and many other physicians and public health experts in the Patient, Consumer and Public Health Coalition, we agree with the FDA's summary report that AEDs are and should remain Class III devices and treated as such going through the PMA process.

And in my last three seconds, I want to say that I want to thank all of you for your work today. The decision you make and the advice you give has the potential for saving many lives. Thank you very much.

DR. HIRSHFELD: Okay. And thank you, Dr. Zuckerman.

Our last speaker, the previously assigned speaker, is Mr. Paul Smolenski, who is the Senior Director for Quality and Regulatory Affairs at Philips Medical.

MR. TRIMBLE: Good afternoon. I guess, first, for a point of clarification, I'm not Paul Smolenski. Mr. Smolenski is over here, and he's my colleague. My name is Vernon Trimble, and I'll be representing Philips.

So I am Senior Director of Quality and Regulatory Affairs at Philips and today, along with my colleague Paul Smolenski, will be providing comments on AED reclassification and Philips' petition to reclassify AEDs to Class II with special controls.

On August 5th, 2009, Philips submitted a reclassification petition in response to FDA's 515 program initiative, requesting that AEDs be reclassified from their Class III pre-amendment status to Class II with special

controls. The petition included a detailed draft version of a special control document to support the Class II designation.

It may be surprising to know that there is a long history of AED functionality being regulated as Class II. For example, arrhythmia detectors and alarms have been regulated as Class II with special controls since 2003, and manual defibrillators, which use the same waveforms as AEDs, have been Class II since 1980.

Special controls are used today for other Class II devices, such as PTCA, the lung catheters, that once were Class III PMA devices and are now regulated as Class II with special controls.

It is our position that special controls for AEDs can be created that will codify the practices developed over the last 27 years between regulatory officials and industry representatives and provide assurances of safety and effectiveness.

The first computer-controlled AED was cleared by the FDA in 1984, which essentially marks the beginning of the modern AED era. Since that time, there have been decades of collaboration and learning among regulatory officials, industry, and clinicians. In fact, it was back in 1984 at the American Heart Association's public access defibrillation conference that the larger clinical community embraced public access defibrillation and momentum began to build.

Many industry standards for AED performance and safety have

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since been developed and reaffirmed, such that the regulatory officials, industry, commission, and users share a common language and expectation.

In addition, numerous clinical studies evaluating the safety and effectiveness of AEDs in various settings and their use by a range of non-clinical responders have been undertaken, and their conclusion and positive outcomes have been published.

For example, a government-funded study placed over 1500 AEDs in public access across 24 U.S. regions, with 19,000 trained lay responders. The study compared survival between responders trained in CPR only to responders trained in both CPR and AED use. The study reported that survival doubled in the AED and CPR users compared to CPR alone and that there were no adverse events due to AED use.

As a result of these learnings, several generations of AEDs have come to market through the 510(k) process. Each generation is increasingly smaller, less expensive for the public to deploy, and easier to use. These technology evolutions have made it increasingly practical to widely disseminate AEDs that help save more lives from sudden cardiac arrest.

The momentum that began in earnest has become reality. AEDs are widely deployed and saving lives. What we can't fail to lose sight of in this discussion about AED classification is that, while AEDs are saving lives today, we are making great progress, but the job is not done.

Sudden cardiac arrest still claims the lives of approximately

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295,000 Americans each year. The sudden cardiac arrest out-of-hospital rate is approximately 80 percent, largely because a defibrillator doesn't arrive in time. AEDs provide an opportunity to help some of those lives that would otherwise be lost to sudden cardiac arrest.

We've heard today that the risk to health is that AEDs will malfunction and this compromises the ability to rescue a patient. It is our position that the bigger risk today is that an AED will not arrive at the patient's side in time to give the person a chance of being resuscitated.

We share the history of working with regulatory officials for decades and the success of the devices out here today, which sounds at odds with the data you have heard this morning about medical device reports and recalls. We take these issues very seriously and would like to offer our perspective of how MDRs and recalls reflect actual field performance of AEDs.

In considering MDRs, it's important to recognize that AED deployment has increased significantly over the past five years. If all else remains equal, this alone could account for the increase in MDRs.

For a clear perspective on MDRs, it's important to understand the medical device reporting regulation and the challenges manufacturers face in applying it to the unique situation of sudden cardiac arrest. The key issue is that the regulation calls for manufacturers to report events that may have caused or contributed to a death or serious injury.

The regulation is challenging, given the nature of the sudden

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cardiac arrest, as even with early defibrillation a significant portion of patients are not resuscitated and don't survive. Therefore, when a defibrillator is used in an emergency, the typical patient outcome leans to reporting because of wording: may have caused or contributed to death or serious injury.

Even with the best information available, determining the AED's impact on outcome is affected by other factors such as the patient's underlying medical condition or the length of downtime before the patient was defibrillated. And often the type of information is difficult for manufacturers to obtain.

What this means in practice is that unless specific information is provided stating that the AED did not contribute to the patient's outcome, manufacturers may have to report it as an event, as an MDR.

Another item to consider is that the MDR database, as you've heard, is comprised of AEDs as well as manual defibrillators with AED functionality, like those used in hospitals, clinics, and emergency services. These are two different device categories that have different use modes and share the same product code. Yet, all reports reside in the same database and, from the information presented thus far, are not analyzed accordingly. Instead, all reports have been attributed to AEDs.

So one issue unique for AED manufacturers, because of the nature of sudden cardiac arrest, is knowing exactly what to report and what

not to report in these situations. This has led Philips and other manufacturers to share the same sentiment as was stated on the December 2010 FDA workshop and adopt a conservative interpretation, may have caused or contributed to a death or serious injury, resulting in us, industry, being overly, aggressively approached in MDR reporting over the last five years.

The outcome of the FDA workshop, as proposed by Philips, will be the development of the FDA guidance document specifically for AEDs and their unique use conditions. Such a document would be designed to bring reporting consistency across the industry, regardless of device classification.

One other point on the MDRs is that hundreds of peer-reviewed studies on AEDs have shown a variety of improvements in survival rates and demonstrated a wider range of responders' ability to operate AEDs. What is interesting is that none of these studies have highlighted problems with the AED or safety issues for patients or users. In fact, PAD trials specifically looked at device issues and determined that they never affected the safety of the patient or lay user.

If the problems were manifested to the degree claimed by FDA, this would have shown up in the clinical data. These issues are currently below the threshold noticeable to the clinical community.

As Shah and others stated in their paper on recalls and safety alerts affecting automated external defibrillators, actual AED malfunctions do

occur occasionally, although the number of observed malfunctions are small compared to the number of lives saved by these important devices.

Much of the discussion has been around design, manufacturing, and the emergency use aspect of AED life-cycle. But when we look at the life-cycle segments of AEDs on a time scale, we see a striking phenomena. AEDs are designed for infrequent use and spend the vast majority of time in a readiness mode. But they must work when needed, as in an emergency. The ability to maintain readiness is a critical function in order to support the widespread deployment. The concept of device readiness, which is called self-test in this application, is central to the discussion of how AEDs are actually performing in the field.

While each manufacturer implements self-tests in their own way, at the highest level, self-test technology enables the AED to perform regular tests on its internal circuitry, battery, and pads. If the device detects a problem such that it would not be ready to respond to an emergency, the AED provides an attention-getting alert.

What is important to understand is that the self-test is designed to detect issues in advance of an emergency situation so that the device can be removed from service. Some manufacturers typically report these as device malfunction MDRs. Without further analysis about when the malfunction actually occurred, generalizations and conclusions about MDR are misleading.

It is important to understand that manufacturers have access to self-test data stored in the device's internal memory, as you heard a minute ago from my colleague Paula from Physio-Control, which can provide insights into actual field performance with this unique type of device.

Self-tests and the data it generates is a valuable tool for ensuring patient safety. The problem is that the critical functionality has not been properly explored with the regulatory community, in order to explore its benefits as a means of understanding actual field performance. We believe the readiness data should be considered as additional safety and effectiveness information, alongside a detailed analysis of MDRs and recalls, as it provides critical information reflective of actual AED field performance.

Self-tests are designed to monitor the actual failure rate. It provides information so that appropriate action can be taken to assure continued device readiness. We believe that manufacturers are already using MDR and other data for trending such that they can take field actions when warranted.

In many cases, recalls are a manufacturer's way of addressing quality issues that are detected as part of the AED self-test, not issues detected during emergency use. Recalls do not necessarily mean that AEDs are actually failing. Self-test alerts are preventative measures.

In addition, sometimes upgrades or continuous improvement activities to AEDs are classified as recalls. When some AED models are

supported for seven years after their first introduction, these actions should not be looked at as a quality or a design deficiency. Recalls are an indication that manufacturers are taking the appropriate action.

There is no common understanding between FDA and industry regarding interpretation of data or expectations for device performance. While other medical devices, for example, ICDs, have recognized failure rates and consistent definitions of key terms like malfunction, performance, and reliability, a similar rate or document had not been established for AEDs. As such, recall thresholds are not consistently applied across the industry.

Another source of data that could be considered to determine whether sudden cardiac arrest patients are being exposed to an additional risk are postmarket surveillance regulatory options, which are already part of the quality system regulations that exist today, such as postmarket studies and registries would be an addition.

Before making a reclassification recommendation, an accurate understanding of the true nature of the issues is imperative. There are many recognized challenges surrounding medical device reporting for external defibrillators, and MDRs should be carefully considered in terms of their value for making safety and effectiveness determinations.

Self-tests support the AED's critical readiness functionality and has been overlooked as a tool that enhances AED availability and safety. Recalls are an indication that manufacturers are taking the necessary steps

and the necessary action. However, there are no recognized standards around device failures, and recall determinations are not consistently applied across the industry, making it difficult to draw meaningful conclusions.

We believe that readiness data should be considered as additional safety and effectiveness information, as it provides information reflective of actual AED field performance.

So we, Philips, believe the biggest public health advantage is deployment of safe and effective defibrillators as expeditiously as possible and that the Class II special controls process, as my colleague Paul Smolenski will now present, will convince you of this.

MR. SMOLENSKI: Thank you. Hi, my name is Paul Smolenski, I'm the real one, and I'm here to talk about -- I'm the Director of Quality and Regulatory at Philips Healthcare, and I'm going to talk a little bit about Class II with special controls.

Before I get started, one point of clarification. I believe it's important for this Panel to understand that life-supporting and life-sustaining devices can be Class II, such as ventilators, for example.

Per the regulation, the real difference between Class II and Class III is what you know about the device. If you have a high-risk device that you don't know much about and you need to regulate it on a device-by-device basis, each individual model, then Class III is appropriate. However, if as in the case of AEDs, if you know a lot about the device, it is a well-

understood technology, then Class II regulations with special controls can be appropriate.

So according to the Food, Drug and Cosmetic Act Section 513(e)(2), a change in the classification of a device from Class III to II can be made if it is determined that special controls would provide reasonable assurance of safety and effectiveness for the device.

We're here to consider the regulatory classification status for AEDs, and special controls are a critical part of that consideration. Special controls can be anything that, in conjunction with general controls, will provide a reasonable assurance of safety and effectiveness.

A little bit of history here. In 1990 special controls became the defining charter of Class II devices by replacing performance standards that the Agency was unable to do in the 14 years that had elapsed since the 1976 device amendments. Performance standards in that original piece of legislation proved to be too resource intensive for FDA to promulgate, and it was believed that special controls would give the Agency broad discretion to select controls necessary to provide reasonable assurance of safety and effectiveness for Class II devices.

Specifically, the Food, Drug and Cosmetic Act states that, to achieve such assurance, special controls may "include the promulgation of performance standards, postmarket surveillance, patient registries, development and dissemination of guidelines (including guidelines for the

submission of clinical data in premarket notification submissions in accordance with Section 510(k)), recommendations, and other appropriate actions as the Secretary deems necessary to provide such assurance."

In other words, to recommend to FDA that AEDs should be placed in Class II with special controls is wholly appropriate and does not create a basis to argue for Class III status because of the challenge of implementing those controls.

Philips did, in fact, submit a draft special controls with our reclassification petition back in August of 2009.

Special controls under Class II would codify the extensive learning experience of the last couple of decades between regulators, manufacturers, and the clinical community. Class III status would enforce tighter controls that do not capture this hard-won experience.

Special controls would raise the best practices bar for the entire industry, capturing the specific lessons of decades of innovation for improving quality and performance.

Special controls will bring together FDA's learnings and unique perspectives, along with those of industry.

Special controls would, for the first time, provide common and consistent language and understanding among FDA and industry.

Okay, stepping back a little bit in the regulatory arena, how do special controls apply to the regulation of AEDs? First, any medical device

seeking market status in the U.S. is governed by certain general controls. And there's a selection of them up there on the slide. These set the ground rules and expectations for manufacturing and selling medical devices of any classification. For example, quality system requirements establish good manufacturing practices to which device makers must adhere regardless of device classification.

For devices intended for marketing under Class II 510(k) requirements, there are additional requirements that add specificity to the submission. For example, manufacturers seeking a clearance for a device must submit detailed device descriptions, theory of device operation, environmental limitations, labeling, et cetera, et cetera, for these devices.

And then, finally, as we submitted in our draft special controls guidance to FDA as part of our reclassification petition, we would welcome the opportunity to work with FDA and the industry to adopt well-crafted special controls for AEDs. I'll now outline some of the key topics in the draft special controls that we provided.

Okay, performance testing standards. The very existence of recognized specific device standards is itself a measure of the maturity of a device in the industry. Performance standards for AEDs are well established. For the last couple of decades, manufacturers, regulators, and the clinical community have jointly evolved standards for the technical performance characteristics of AEDs. For example, DF80 provides a strong and technically

sound basis for AED performance and safety testing.

DR. HIRSHFELD: Excuse me, Mr. Smolenski.

MR. SMOLENSKI: Yes?

DR. HIRSHFELD: Are you close to wrapping up, I hope?

MR. SMOLENSKI: I am more than halfway through.

DR. HIRSHFELD: Okay. Well, you're already a minute over your allotted time.

MR. SMOLENSKI: Okay, I apologize.

So I'll very quickly go on to risk assessment. An important aspect of all special controls is the requirement to foresee and mitigate potential hazards associated with a device through its life-cycle. This analysis can be based on recommendations of established standards that are used to market devices in Europe, such as the risk management standard. This standard describes the process for performing a risk/benefit analysis, including identifying the risks and their causes, mitigations implemented to address these risks, and categorizing the level of residual risk.

In addition, these same processes could be applied to key components, supplier controls, and supplier management included in AED special controls.

It's important to note here that the risks for AEDs are well known and, at least in Philips' experience, have been remarkably consistent since the mid-1990s.

The next point in the special controls document has to do with user requirements. To achieve the widespread availability of early defibrillation, manufacturers have tailored their devices for use by a wide variety of users, from professionals to lay responders. Much design and validation effort goes into assuring that AEDs can be used successfully by their intended users. Accordingly, special controls should require that manufacturers demonstrate in detail how users are defined and how appropriate usability has been achieved.

Readiness for use; already displayed this information that many devices spend the bulk of their time in a readiness state. It's an intensive design topic of manufacturers and is well suited for consideration in special controls. Performance in the readiness phase is of particular importance for both manufacturers and regulators. Drafting an effective special controls document on this topic could achieve better alignment between industry and regulators on interpreting AED data from the readiness phase.

As you weigh the classification question, it is important to consider the implications of this decision. As FDA has identified, Class III designation may have unintended negative impact on public health, including slowing the pace of innovation and increasing the cost of deployment. So of those AEDs used outside of professional markets, AEDs are a price-sensitive product. There is no insurance coverage to purchase them, so businesses, schools, communities, and businesses have to fund these programs

themselves, sometimes even through things like bake sales and other grassroots fundraising.

Given the price-sensitive nature of AEDs, it is likely that outcome would be fewer AEDs disseminated, which ultimately translates into fewer opportunities for the AED to be available when one is needed to help save a life.

It is our position that Class III will ultimately limit access to AEDs. However, Class II with special controls provides an opportunity to capture the learnings of regulators and industry from the past 27 years and consistently apply these best practices across the industry. This pathway provides an appropriate assurance of safety and effectiveness, along with the opportunity for AED technology to continue to keep pace with the resuscitation science and ensure that such innovation continues to reach the public in a timely manner.

Last slide. AEDs have been intensively developed and studied over the past quarter century and are safe and effective devices that are saving lives. Over that time, the industry, clinicians, and the public have found that AEDs don't always fit the mold for the way things are usually done. However, together we have figured out how to realize the goal of widespread deployment of AEDs as we had moved from professional to lay users, monophasic to monophasic waveforms, from big heavy devices to ones that are lightweight and portable. Together we worked through these challenges

because they were the right things to do to give sudden cardiac arrest victims a better chance at resuscitation.

Today, there are legal existing regulatory pathways that can be adopted to continue assuring the safety and effectiveness of AEDs and that reflect these hard-won experiences, namely, special controls. We view Class II with special controls not as the status quo, but as an opportunity for improvement; special controls would facilitate common understanding and expectations between regulators, clinicians, consumers, and industry.

We also believe the regulatory oversight tools exist today that can be incorporated into special controls to provide reasonable assurance to the stakeholders that AEDs are safe and effective. This is the best way to improve the regulatory status and continue the widespread deployment of these lifesaving devices.

Thank you.

DR. HIRSHFELD: Thank you. Right, we have three other speakers. The first will be Katherine Crowley from Defibtech. Is she here? It looks like we just picked up the five minutes that we lost.

Okay. Then the next one is Dr. Michael Carome, Deputy Director, Health Research Group of Public Citizen. And, Dr. Carome, you have five minutes.

DR. CAROME: Good afternoon. My name is Dr. Michael Carome. I'm the Deputy Director of the Health Research Group of

Public Citizen. I am testifying on behalf of myself and Dr. Sidney Wolfe, the director of our group. We have no conflicts of interest.

There have been a total of 68 recalls of AEDs from January 2005 to August 2010, 17 of which were serious enough to be Class I recalls, the most serious type of recall, involving situations in which there is a reasonable probability that using the product will cause serious injury or death.

Despite this, the AED industry, with the nine companies seemingly in lockstep, has asked the FDA to deregulate these life-supporting devices so as to avoid the requirements that they be tested more thoroughly by remaining in device Class III.

On January 13th, 2009, Public Citizen wrote to the FDA about one such Class I recall initiated by one of these companies, Welch Allyn, involving 14,054 of its AED 10 and MRL JumpStart defibrillators, the largest of several recalls of these dangerously problematic Welch Allyn devices to date.

This recall was for the following problems listed in the table on the screen, each affecting varying numbers of the total of 14,000-plus recalled units. The table identifies the problem leading to the recall of those units, the number of affected units, the date manufactured, and whether or not serious injury or death was reported by Welch Allyn.

Welch Allyn acknowledged that two deaths were associated with problems identified in this recall. According to the FDA website, in January 2008, a patient died after the AED 10 shut down in the middle of

resuscitation. Then, in November 2008, a patient died after an AED 10 failed to shock during resuscitation.

In our letter we asked FDA to promptly respond to the following questions: How are manufacturers deciding which devices are affected and are subject to the recall? Moreover, why did FDA not announce this recall at the time? Furthermore, why is FDA permitting manufacturers to continue to introduce these potentially lifesaving devices with only minimal data through the 510(k) pathway?

FDA has yet to respond to our letter in any substantive way, but today's hearing does squarely address the last of these three questions.

The entire category of AEDs, a Class III medical device, has been insufficiently regulated by the FDA. Class III devices are life-supporting, life-sustaining, of substantial importance in preventing impairment of human health, or present a potential unreasonable risk of illness or injury.

Because of their risk, Class III devices are to be regulated under the premarket approval PMA pathway. This requires direct evidence of safety and effectiveness before being marketed. However, because the FDA has failed to meet statutory requirements established in 1990, AEDs and a handful of other types of Class III devices are still regulated under a less stringent premarket review mechanism, the 510(k) pathway. Thus, the amount of data, specifically clinical data, submitted by manufacturers prior to marketing AEDs is sparse.

While AED manufacturers seek to maintain the status quo, such a position fails to adequately protect the public health.

The FDA has asked the Committee whether AEDs should be reclassified from Class III to Class I or II. We urge the FDA to maintain AEDs as Class III and require all AED manufacturers to submit new PMA applications to FDA and obtain FDA approval in order to continue marketing their devices.

AEDs are lifesaving devices used by emergency responders, as well as minimally trained and untrained individuals, in a variety of settings outside of hospitals. However, the FDA over the past five years has identified numerous, persistent, preventable safety problems with all types of AEDs across all manufacturers of these devices.

FDA's review of performance testing data has identified numerous troubling failures by AED manufacturers. The number of recalls per year in the period 2005 to 2010 has increased dramatically.

Finally, FDA analysis of MDRs in the MAUDE database identified 23,000-plus MDRs for the time period January 1st, 2005 to March 31st, 2010, including 721 deaths, 78 injuries, and more than 22,000 malfunctions, among others. The total number of reports have substantially increased over the past five years. More importantly, approximately two-thirds of reports of failed devices never report a root cause and are never evaluated by the manufacturer.

In closing, a recommendation. In the interest of protecting

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public health and promoting innovation, it is imperative that FDA reject industry wishes and instead maintain the Class III categorization of AEDs and require AED manufacturers to submit PMA applications. Such applications must include data from robust clinical trials that reasonably assure that AEDs are safe and effective.

We also note that the status quo essentially represents ongoing, uncontrolled human experimentation with no ethical oversight.

Finally, I note, in response to the FDA staff member who presented the minority view of the Agency, he noted that a clinical study takes a long time and poorly designed or poorly conducted studies could raise new concerns and further delay introduction of new AED technology. I must say, I have never heard a more ludicrous argument against conducting clinical trials to assure the safety and effectiveness of medical devices.

Thank you.

DR. HIRSHFELD: Thank you. Our final speaker is David Belkin, representing the Sudden Cardiac Arrest Foundation.

MR. BELKIN: I don't have any presentation, in terms of anything for you to read ahead of time, because we received word late.

I'm David Belkin, and I'm a member of the board of directors of the Sudden Cardiac Arrest Foundation. And our mission, according to the letter that we did submit to you, is to raise awareness and support programs that give ordinary people the power to save a life.

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Now, I'm not a scientist, I'm not a doctor, I'm not a researcher, and I want to talk to you a little from the point of a non-theoretical point of view. There's a human element, and that is I'm talking to you as a survivor. I survived sudden cardiac arrest out of hospital, and I was saved by an AED.

So I'm reading from the Executive Summary here that states, "The risk to health associated with AEDs is that these devices can malfunction. The failure to deliver a defibrillation shock to a patient in VF or pulseless VT can result in permanent injury or prevent the rescue of the patient."

I wish there had been a statement in here that said the greatest risk is to have people die that do not have to die when there is a device that can save a life. To me, that is even a greater risk. If there is a device that is available to save a life as the AED saved mine, then I think it should be utilized, notwithstanding the fact that there are malfunctions.

There are 295,000 cases annually of out-of-hospital cardiac arrest, and only about six to seven percent of the folks suffering SCA are saved. I'm happy to report that the percentage is climbing because of the proliferation of AEDs in airports, health clubs, schools, public buildings, as your Executive Summary notes.

And education is a big factor in this. And as somebody noted this morning, the key is public access defibrillators. Having access to defibrillators in airports, health clubs is to me key. And education. That is

why it works so well in Seattle, where you have the highest percentage of survival from out-of-hospital sudden cardiac arrest.

I don't know of any cases where a defective AED has injured someone whose heart has stopped beating as a result of an SCA. Now, I've read the report that there are malfunctions and there are cases where potentially the person died, but we don't know whether it was because of the malfunction or whether it was because the person could not have been revived in any event.

In fact, I asked my executive director about this, and she said, to her knowledge, the problems that have been related to the failure of the AED to work properly and thus failed to resuscitate someone has not caused further damage.

There are reportedly one and a half to two million AEDs in service according to estimates. So the times AEDs have not worked properly is a fraction of this total. I believe the 23,000 figure in your report or in the FDA report is a fraction of the total number of AEDs that are in service.

I'm not being facetious about saying that having a defective AED can make a tragic situation worse. In other words, had there not been an AED at the school where I collapsed, I might not be here talking with you this afternoon. So I'm not sure how you can say or it can be said that someone who essentially is dead can be worse off with having an AED, notwithstanding the fact that it might be defective.

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These devices are life-and-death devices and cannot be compared to prescription drugs, which need to be regulated. But the prescription drugs are not devices that can immediately save a life.

The AED that was present at the school after I had my collapse was put on me within three minutes. Had I had to wait for either an EMT crew or get to a hospital, who knows what would've happened? But the fact that it worked was fine. If it didn't work, at least it was there and that, to me, is the issue.

So AEDs are truly unique devices, and I believe that they should be treated as Class II devices with unique controls. Thank you.

DR. HIRSHFELD: Thank you. Okay, we're now going to have the opportunity for the Panel members to query any of the speakers who spoke in the last hour and 15 minutes.

So Mr. Dubbs.

MR. DUBBS: I'd like to ask the manufacturers individually to respond to this question. Can you give us specific concrete examples where, within your organization or in organizations that you're familiar with, that a regulation has stymied innovation and product development for your companies?

MS. LANK: Paula Lank, representing Physio-Control. A more general example I would put forward versus specific is that we are, on a consistent basis, able to market products in Europe, the European Union,

sooner than we can market them here in the U.S. because of the regulatory approach. It's different and we launch here in the U.S. some period of time after launching in Europe and other parts of the world.

MR. DUBBS: Yes, but we're talking about an AED that your company manufactures. Can you give us any specific concrete evidence that this has happened?

MS. LANK: Recently we launched a second iteration of a device called the LIFEPAK 15. We added temperature measurement and both a capacity for AC power, plug it into the wall to the hospital, and DC power for ambulances. We CE-marked the device earlier in 2010 and are now shipping that product into Europe and other parts of the world, and the 510(k) is still pending on that product today.

DR. HIRSHFELD: Dr. Zuckerman.

DR. B. ZUCKERMAN: I'm glad that the comparison with Europe has been brought up by the industry representative because Europe is often referred to as the gold standard by the industry because of the device lags that are quoted. I think it's very important for this Advisory Panel to understand the bigger public health picture in Europe.

At the end of this week, the European Society of Cardiology will have a special two-day meeting on device approval process in Europe. FDA has been asked to be a contributor to that meeting because of recognized problems in Europe.

So I'm not saying that any one system is perfect by far. But the notion that Europe somehow has perfected the system, I think, has a lot of question marks right now, and we look forward to our participation in the European Society of Cardiology conference.

DR. HIRSHFELD: Yes, Dr. Kelly.

DR. KELLY: So the point has been made, particularly with the MDRs, that we really don't know how many of them had to do with the simple bystander devices in airports and schools versus the more complicated devices in hospitals.

But for the recalls, I would imagine the companies have that information. Do you know, with your company in particular, how many recalls were the publicly available devices versus the more complicated ones in the hospital?

MS. LANK: I don't know off the top of my head. My guess is that there may be more recalls in just standalone AEDs and there are more AEDs in the installed base in the U.S. and certainly around the world. So part of, I think, the challenge is the number of devices that are part of any one given recall. If it's a standalone AED, it can be quite large because they are broadly available.

DR. KELLY: Right, but not number of actual devices, just --

MS. LANK: Um-hum.

DR. KELLY: -- types or models.

MS. LANK: I really can't tell you without -- you know, I'd like to give you current and accurate information and --

DR. KELLY: Okay.

MS. LANK: -- I can't comment.

DR. KELLY: And how about from Philips? Are you Philips?

MS. LANK: No, Physio-Control.

MR. SMOLENSKI: Recalling this information from memory -- I would like to confirm it -- in an analysis of recalls that we did internally from a briefer time period, 2008 to present, we had slightly more individual recalls in the advanced defibrillator/monitor space. Our experience has been, with these devices, that they see a much rougher use model, particularly in EMS, and sometimes that can create some reliability and usability issues in terms of our hardware.

DR. KELLY: Okay, thank you.

MR. DUBBS: Could you respond to the question I asked from both companies, about specific examples?

MR. SMOLENSKI: We do not have a specific example that comes to mind at the moment, where the difference in regulation has stymied innovation, although I do resonate with your conclusion that we tend to find the path to market in Europe a little bit more workable.

DR. HIRSHFELD: Yeah, Dr. Page.

DR. PAGE: Thank you to all the presenters. I share the last

presenter's concern that these devices be available when they're needed. I obviously want them to work when they are employed.

My questions are to Ms. Lank and Mr. Smolenski, from Physio-Control and Philips, respectively. And both of you had points that I think are concerning in terms of what you see the PMA process would do to the availability of AEDs. We want AEDs out there.

So let me ask you what you estimate. Say, fast-forward and hypothetically the outcome of our recommendation and more importantly the outcome of the FDA's decision is that these be regulated as Class III devices. You will have, I understand, 12 to 18 months to develop a PMA to at least cover the devices you have in place. My question is, would you see a delay in these devices being available?

And my second question is now fast-forward and we've reached steady state and we're all living with this Class III designation. You both mentioned that you're fearful that the cost of AEDs would increase. Have you done the math to tell us what the change would really be per device, as you think this may have an effect on more broad implementation of this technology?

So the first issue is can you put together a PMA so we don't lose the throughput, and the other is what's the real cost per device, as you see the future?

MS. LANK: As I mentioned, the PMA process will double or

triple the time and --

DR. PAGE: No, no, that wasn't my question. The issue of innovation is not my question.

MS. LANK: Right.

DR. PAGE: My question is, right now we have good devices out there. There just aren't enough of them out there. So I'm concerned that they be available.

So do you truly see an interruption of delivery of -- can you make a deadline that -- my understanding from Dr. Zuckerman was that it would be about 12 to 18 months, Bram, is that right, for the hypothetical PMA, if we went that direction?

DR. B. ZUCKERMAN: Yeah, and I'd like to answer your excellent question after the industry does.

DR. PAGE: So, again, my question is the devices we have -- don't tell me it's got a new temperature sensor. I want a device that shocks the patient out of ventricular fibrillation, but I don't want the throughput to be interrupted. Can you meet this if the result is that you have a Class III designation?

MR. SMOLENSKI: It's a very difficult question to try to answer, but perhaps a little perspective. Two of the seminal trials in this industry, the public access defibrillation, or the PAD trial, and the HAT trial took three, four years for the trials to run because it's very difficult to identify your patient

population ahead of time. You don't know who's going to have a sudden cardiac arrest event where the AED will be there.

And so getting the study sizes to an acceptable threshold could be very difficult. I suppose it would depend very much on where the Agency established that threshold of acceptability.

DR. B. ZUCKERMAN: Okay, let's interrupt a moment.

DR. HIRSHFELD: Yeah, let Dr. Zuckerman comment, please.

DR. B. ZUCKERMAN: Because I realize that this puts the industry, and most importantly the clinical community and patient community, in an uncomfortable position.

The first thing is the 12 to 18 months is designated after the final rule is published. So it's probably a longer period of time. But I want to assure everyone that, again, the comments made this morning by the FDA will hold.

There's no question that these are life-sustaining, life-supporting, incredibly useful devices. We're not going to take every device off the shelf. Our goal would be, if the Panel moves in a Class III designation, to find a workable solution, meaning that I would hope the industry would approach the division and branch soon after this meeting to understand what our data requirements are. And I think we have a reasonable idea. We would also utilize expert Advisory Panel members hopefully, like Dr. Page, to weigh in.

So this is a doable process, Dr. Page, and in one respect, it's the -- the complexity is less than the 510(k) with special control process. But that's just a personal opinion right now (a); (b) you asked the question about actual costs of these devices. Well, that's a very interesting question. The Agency doesn't involve itself with the actual monetary costs, rather than public health costs, so that our final decision needs to be based on a risk/benefit decision here, based on science but independent of the actual monetary costs. That's the most useful information that you can provide us with.

DR. PAGE: Right, I understand our obligation is safety and effectiveness, and all things being equal, I think these devices are safe and effective to the degree that's acceptable right now. The reason I did address cost in this case is because it is being brought up and it's hard to completely remove ourselves from that in the setting of this discussion. But I understand your request and will abide by it, that we'll avoid discussion of cost.

DR. HIRSHFELD: Dr. Lange.

DR. LANGE: Go ahead, you first.

DR. HIRSHFELD: Dr. Jeevanandam.

DR. JEEVANANDAM: So I got, you know, a question, and I think, as everybody said, these devices are safe and effective to get you out of V-fib or V-tach when they work, and the real question to me is to make sure that they're maintained so they work.

So as industry, you know, you're starting to sell a lot of these over the counter and in the catalogs, et cetera. Is there a registry kept of all the ones that are sold?

And if I have one at home, for instance, and it does a self-test and it doesn't work, is there a mechanism to get that replaced as soon as possible? And is that something that's tracked?

I think those are -- to me, that's a major question. I have no doubt that these things work. The question is will they work when you need them to work?

MS. LANK: I have three points. We have an obligation by the quality system regulation to do device tracking of every device that we sell, which we do.

We also believe that if a device doesn't work or if it's found to have an indicator on, saying, you know, I need some attention or maintenance of some kind, the people are going to contact the company and make sure that they get a device that's working.

One of the last comments at the defibrillator workshop that took place in mid-December, one of the topics was a national AED registry, and it's my understanding that FDA is going to partner with a researcher at the University of Colorado and over the course of the next year do a one-year plan to implement a pilot project in three cities in the U.S. to establish a national AED registry.

So that will be, you know, sort of the first attempt to try and build a pilot to see if it's feasible and then to tweak it and then potentially to take that registry on a national basis.

DR. JEEVANANDAM: So if all of these are already registered, then why do we not have a denominator according to the MDRs? We should know exactly how many we've sold.

MS. LANK: That information is, I would say, proprietary, and it's -- we're actually attempting, maybe through a third party, to try and get an actual number because we agree strongly that a denominator is needed to put the data into the right context.

DR. JEEVANANDAM: So, Dr. Zuckerman, I have a question for you. If this ends up becoming a Class III device, would that type of information in the annual review be something that the FDA would have access to?

DR. B. ZUCKERMAN: If these mechanisms can be instituted, such as the national AED registry, there would be the possibility for post-approval study data to be ported from that registry to FDA for requirements. Sure, there are a lot of possibilities at this time.

DR. JEEVANANDAM: Would that be possible only if it was -- let's say it would be mandatory if it was a Class III device. But if it was a Class II with special conditions, would it be mandatory or would it be voluntary or how would that work between those two classifications? Because that's what

we're here to decide.

DR. B. ZUCKERMAN: Okay. And I would again encourage you to go back to, I believe, Slide 74 and 75, which show the multiple challenges that we have right now.

But the bottom line is, with the PMA system, asking for a condition of approval study, preapproval can be part of our standard operating procedure. With a Class II system, we would need to ask for a Section 522 study each time, individually. So it would be somewhat burdensome.

And I think there is a theme that we generated today, where, yes, many of these things can be done in a Class II system, but (a) it involves a lot of regulatory work. It's not going to be done overnight (a). And (b) what do you get at the end of the day, other than perhaps a PMA?

DR. HIRSHFELD: Okay, Dr. Lange, you've been waiting patiently.

DR. LANGE: It's okay. To our industry representatives, three questions. One is it's been reported that 66.5 percent of MDR reports do not have any manufacturer evaluation, and if you could explain that.

Two is I'd like for you to explain your recalls with your personal company. 2008 to 2010 with Physio-Control, and yours as well. And I want to know who initiated that. Is that based upon self-tests initiated by the company, or was it initiated after an FDA investigation oversight?

And my last question is, there's a 2006 report or an article that

reports that 20 percent of AEDs failed because of software problems, electrical problems, and this was four years ago. I'd like to know what your company's doing differently as a basis of this report.

MS. LANK: So I'll answer the first question first. And this has been mentioned before. It can be challenging to get a device back to actually evaluate it. Either the institution or the EMS agency doesn't want to let it go, especially if there might be a potential use error that occurred. There could be a concern about litigation, and so they don't want to take that device and send it back to the manufacturer.

We work very hard to get every device back in this country that has a failure or malfunction so that we can evaluate to what we call root cause and not just rely alone on the symptoms that are reported by the customer but really understand, you know, what led to this malfunction or potential malfunction so that we can then address that, we can trend it, put it into our CAPA system, and on a monthly basis we look at this information and decide when and where we need to take action.

MR. SMOLENSKI: We follow basically that same pattern.

DR. LANGE: And for the recalls you've had, the LIFEPAK 500 recall in 2008 and 2010, can you talk about that?

MS. LANK: The LIFEPAK 500?

DR. LANGE: Uh-huh. I just mentioned that because there was a slide here that showed a recall in 2008 and 2010 for Physio-Control LIFEPAK

500 CE, if I'm not mistaken.

MS. LANK: You know, I don't recall if we did a recall on LIFEPAK 500 in the last two years.

DR. LANGE: All right. And what are you all doing differently based upon the report of 20 percent failure rate four years ago? Company-wise.

MS. LANK: I'm not familiar with the report that you're referring to.

DR. LANGE: Okay.

MS. LANK: But design controls --

DR. LANGE: Or a study.

MS. LANK: -- is a very disciplined, rigorous process for developing products. It involves a cross-functional team within the company, with a stage-gate process.

So initially you develop the concept, you develop the product requirement spec, you develop the user needs, the intended environment, and decide what suppliers you're going to partner with, and start the development and the design of the device. And software development is a big part of that.

So in parallel, you're developing hardware and software, and then there's a very important point where you integrate the hardware and the software.

And we go through -- and I'm sure Philips does, as well -- very rigorous verification and validation testing where these products are cycled thousands of times through automatic testing equipment and different environmental situations to confirm if they meet voluntary performance standards which we claim compliance to.

And, then, when each product is manufactured on the assembly line, it goes through very rigorous power-up/power-down charging, probably delivering somewhere between 50 to 75 shocks on every device before it goes out the door. And if there's a failure, then that device is removed from the assembly line and it's taken away to a troubleshooting bench and analyzed to determine what the issue is.

DR. LANGE: So the recalls have been initiated by you all's company based upon internal data and information or based upon FDA investigation or oversight?

MS. LANK: In our experience, it's predominantly internal. We recognize an issue, we decide to take a recall, and then we notify, per 806 reporting requirements, FDA that we're taking that action.

MR. SMOLENSKI: I think it's important to note that the recall volume in some respects reflects a very aggressive approach by the industry to act responsibly to remove not only the devices that are somehow in violation, but also we look very hard at what devices next to those could be involved as well, and we would rather over-recall than under-recall.

They're expensive and they're destructive. It also has an impact on our customers because we will have to swap out these devices for them. There's pain all around. But even then, as has been said here, the number one goal here is effectiveness and patient safety.

DR. B. ZUCKERMAN: Okay, this is a very interesting discussion that we're going to need to continue, but our format has become not what it's originally designed for. It should not be a Panel discussion just with two industry representatives, and I'm going to ask the industry to step back and come up to the podium when they're asked specific questions because I do see Dr. Zuckerman has been trying to get into this very important conversation, and I'd like to take a time out for her to comment, as well as if anyone on the FDA review team wants to comment at this point, and then we can continue.

So Dr. Zuckerman.

DR. D. ZUCKERMAN: Thanks very much. I just wanted to comment because I think the slide that you were referring to was my slide. And we got the information from the FDA website, and it did show Physio-Control LIFEPAK CR Plus being recalled in July 31st, 2009 as well as August 28th, 2008, so the same device recalled twice. But it sounded like the speaker from the company didn't remember that recall, didn't recall that recall. So I just wanted to say that's where we got it from. We got it from the FDA website.

And I guess just to reiterate that I think what's been said, I don't think any of these public speakers are saying, you know, we want these devices off the market. Of course we don't. They're lifesaving devices when they work. But some work better than others, and if you have a better and more stringent process, then you'll have AEDs on the market that are more likely to work when you need them and less likely to fail when you need them.

So any questions?

DR. HIRSHFELD: Yes.

DR. LoGERFO: In your analysis earlier, has there been any instances where anyone was hurt by the device when it shocked, either the patient or bystanders, and are there warnings about this, or is there no danger?

DR. D. ZUCKERMAN: I can only say that we looked at some of the MAUDE reports, but we did not look at all of them, so I didn't have that information.

I do want to add, though, I think it's important that, you know, of course we want these devices to work, and when they don't work, not only does the -- there are two victims, at least, the person who might die or be harmed, but also the person trying to help them in what seems like a nightmare situation where they have a product that they think they're screwing up and sometimes, you know, they're not the ones that aren't doing

it right. It's the product that doesn't work. And, obviously, when it's a policeman or an emergency technician doing it, that's one thing. When it's a family member, you know, it's really very traumatic.

DR. HIRSHFELD: Mr. Simon.

MR. SIMON: Thank you. For anyone who wants to comment. With regard to recalls and self-testing by locations, is there a time frame, a minimum and maximum time frame, whereby the device has to be mailed back and the companies will mail them back within a day, within a week, so that there is a device available to be used?

MR. TRIMBLE: Vernon Trimble, Senior Director of Quality and Regulatory Affairs with Philips.

The answer is, there's multiple channels we can do to recall a device. We use service technicians that we have that are available throughout the U.S., and we also contract with some contractors outside of the U.S.

So one vehicle to use is to do the service at the time in the field, and another opportunity is to have the unit mailed back in, providing that we can get the replacement parts available as soon as possible. So all aggressive means would be taken any time there's a field action or recall.

MR. SIMON: Can you give me a time frame? Is it a day or a week that there's no AED available?

MR. TRIMBLE: I can't specifically give you a time frame. I

would say that we would work with those customers. We would find out their need. We would find out how many AEDs they have as backup, et cetera, and we would accommodate them by working with them.

MR. SIMON: Okay.

MR. SMOLENSKI: A clarification for a customer-owned AED that is involved in a recall action. We will mail them a new device before they send back their recalled device.

MR. SIMON: Okay.

MR. SMOLENSKI: So there should be zero downtime.

MR. SIMON: Okay, I've got two more questions, if I may. I looked on page 19 of the FDA report with regard to malfunctions. There's 6175 in 2010 and 6489. Is that because it's not a full year, or is that because there were less malfunctions? Were there more or less?

MS. SULLIVAN: We can answer that, but I don't have the slide number in front of me. But the analysis by the different problems that we did --

MR. SIMON: Yes.

MS. SULLIVAN: -- device problems, evaluation codes, and results, that analysis stopped on March 31st, 2010. Just to give everybody an idea, for the calendar year 2010, I got the preliminary number of whatever it was, 65 --

MR. SIMON: Sixty-one.

MS. SULLIVAN: -- for the calendar year, but the entire 2010 reports were not included in the further analysis.

MR. SIMON: Okay, okay. And the last question, I guess, to the representatives. I still don't have a handle on why there are deaths and who caused the deaths. We're looking at the deaths again in this report, on page 19. In 2009 it was 184. In 2010 it was 279.

My question is, if 278 of those were because the device caused the death, or if there's one caused because a device wouldn't work, I still don't know if it's a problem because I don't know what that 279, or the previous deaths, what that represents.

MS. LANK: We don't fully know, but what was represented today, this morning, is that of the MDR reports that are in that analysis, 97 percent are associated with malfunction. Ninety percent of the 97 percent were not during patient use. They were detected either through self-test or user test. Of the three percent that had a reported adverse event, the majority of those, as FDA said this morning, the reporter indicated the device did not cause or contribute to the patient outcome.

So now, you know, whatever that is, one percent of those deaths would've been reported as associated with a contribution to the patient's outcome.

MR. SIMON: I'm not sure I understood that. Of the 279 in 2010 --

MS. LANK: Um-hum.

MR. SIMON: -- what was as the result of the use of an AED?

MS. LANK: I can only recount what was communicated this morning. It's a very complex series of steps to go through and understand what role did the AED really play in the death. I think that's information that we could better characterize and collect to understand in the future. And part of the initiative of working with FDA and industry is to do that, is to collect more detailed information about each of these events so that we can understand what that correlation is.

DR. HIRSHFELD: Okay, we're going to need to move forward at this point. Did you have a quick comment?

DR. D. ZUCKERMAN: Yeah, I just wanted to say, on the data that we looked at, if it's reported as a death, it's because the person died usually because the product didn't work. So, yeah, maybe they would've died anyway and you can't always tell.

Well, we looked at the MAUDE reports to see what they said, and I gave some examples where the product didn't work, the person kept trying to get it to work, it didn't work, and the delay between using the product that didn't work and getting help in some other way, the person had permanent damage or died.

MR. TRIMBLE: Vernon Trimble with Philips. I just want to respectfully disagree with the comment just made.

As the regulation requires, any time that a medical device, and specifically an AED, is involved in an incident where a death occurs, where a death occurs, whether the AED contributed to it or not, we report it as an MDR. We report it as an MDR. And it's very difficult, as we've said numerous times today, to ascertain critical information and the analysis of that to determine if indeed there was any type of functionality issue with the device.

DR. HIRSHFELD: Are you saying that every time there's an unsuccessful resuscitation attempt in which the AED was used, that you report that as an MDR?

MR. TRIMBLE: If the patient expires. If the patient expires, unless we have some written confirmation from the clinician that says that they know for a fact the AED did not contribute to it, we report it. And that's why we've talked a lot about the MDR information being misleading.

DR. HIRSHFELD: Yes.

MR. MacFARLAND: We'd be happy to provide clarification from FDA on the submission and analysis of deaths, if you would like.

Luke.

DR. HIRSHFELD: Okay, if it can be brief because we've got some more work to do in the next 40 minutes.

MR. RALSTON: I would like to acknowledge that the definition of a death report sometimes is not as clear as we would like it to be and that there are numerous reports that we receive every year that say something

along the lines of the device malfunctioned and the patient died, but the clinician stated that it was not as a result of the device. And, yet, they still choose to submit it as a death report.

So, in those cases it would appear as though most of the companies are taking a conservative approach and reporting as a death report something that might possibly be a death. It's very rare, as the lead reviewer of these devices, that I see the opposite, where it would a malfunction that looks like it might be a death. So I don't know if that clarifies the issue at all.

But one of the more complex parts of this issue as a whole is that the normal outcome of defibrillation, I believe, something like two-thirds of the patients who are defibrillated die anyways. And so to try and have a good hard and fast definition of what constitutes a death in every situation is not always possible.

DR. HIRSHFELD: Let me just ask you to be very clear on one thing. So what you're saying is that the number of all of these reports that we have that include deaths, that only a very small fraction of them are reports of a nature that the device was activated, the device failed to work, the patient died. Is that what you're saying, that that actually represents the minority of those MDR reports that are classified as deaths?

MR. RALSTON: Generally, the death reports are the reports that the sequence of events is exactly how you just described. Even if the

clinician --

DR. HIRSHFELD: No. So I've been getting mixed messages on this. One message says that all of the death reports or actually many of them are just -- they're really not related to a device failure. And then other people are suggesting -- and what I'm trying to figure out is that the deaths that we know about, that you reviewed the case reports of, were they deaths in which an attempt was made to use a device and the device didn't function properly and the clinician may have decided that that wasn't necessarily the root cause of the death, but still that there was a device malfunction in the act of trying to resuscitate somebody?

MR. RALSTON: I would say, in almost all cases, yes.

DR. HIRSHFELD: Okay. David.

DR. NAFTEL: A couple things. The next time we have this discussion, which we will, it would sure be nice if the Panel had in front of them a copy of the Form 3500A so you could see exactly how the question was asked, and then you would understand there's so many interpretations.

The second thing -- and perhaps FDA will correct me, I hope you will. But I think when I've worked with you with MDRs before, that you're slow, in fact totally resistant, to do any interpretation of MDRs. Like you could've gone through all of these MDRs and said normal process, no device contributed to death. You could've done some sorting out. But I think you don't like calling what you say are interpretations. I think you don't like

going that far, but it sure would help us, if you would. So please tell me I'm wrong.

MS. SULLIVAN: You're looking at me now. You're wrong. It's difficult, obviously. You can maybe get categories, probably, probably not, not enough information to tell. You know, as we do our routine surveillance and looking for new signals, there has to be a certain extent of that. It's just, as you can imagine, very difficult to make definite causal relationships between or temporal relationships between a device and an adverse event.

I heard what one company said. However, if we receive a death report, it's because -- we have to assume it's because they believe that their device may have caused or contributed to the event.

DR. NAFTEL: So tell me why I'm wrong, then.

MS. SULLIVAN: Well, you said that we didn't like to try to analyze them and understand them.

DR. NAFTEL: But in this case you didn't make any attempt. If it's a death, it's a death. I mean, you didn't sort it out.

MS. SULLIVAN: That's true. I thought you were talking about in general, just for everything.

DR. NAFTEL: Well, maybe in general, but I really meant to this case.

MS. SULLIVAN: Sure, okay, sorry about that.

DR. HIRSHFELD: I'm going to take the Chair prerogative now to

get us back on task. Our next task is for the Panel to deliberate and react to the information that we have heard thus far. This is in advance of what will happen following this, which is when FDA will actually submit the questions that they want the Panel to address.

So what I'd like to do now is I'd like to hear the Panel's reactions. I'd like to hear from everybody. And I don't want to be the grim reaper and go around and single out people, but I'd like people to volunteer and just give us their thoughts about where they see our understanding of this knowledge base at this point. Who would like to start?

Okay, Mr. Swink has just reminded me that I have close the Open Public Hearing, which is closed. Thank you.

All right, now we'll go to our deliberations.

Yes, Dr. Karasik.

DR. KARASIK: Thank you. I think I'm more confused now than I was at the end of the morning session. But I guess the only thing I'd like to say right now is that I sort of want to point out that companies have been producing AEDs for more than the past 20 years under the Class III classification with the 510(k) process. Right, that's how all the AEDs are out there now. And we're talking about how the MDR system isn't so great and maybe we can improve it.

And I'm asking, well, where have you been for the last 20 years, and why are we having all of these problems? You had opportunities to make

all of these improvements, so it strikes me as somewhat disingenuous to say, well, now going forward, we're going to operate under a similar regulatory guideline, only as a Class II with the same 510(k) process and we're going to be better, and that just bothers me a bit. I'm going to throw that out there.

DR. HIRSHFELD: All right, thank you. All right, I may have to be the grim reaper if people don't volunteer.

DR. PAGE: John, are you asking for --

DR. HIRSHFELD: Yes, I'd like --

DR. PAGE: -- our decision as to classification?

DR. HIRSHFELD: No.

DR. PAGE: We're putting it all together now or --

DR. HIRSHFELD: No, just putting -- the purpose of this is to put together what we have heard thus far, in terms of how we -- what we feel about the knowledge base that has been presented to this date.

DR. PAGE: And looking for conclusions based on what we've heard?

DR. HIRSHFELD: Yes, moving in that direction.

DR. PAGE: Okay. First of all, AEDs are phenomenally important devices. I wish there were one in this room. They save many more lives than they harm. I believe the companies have been innovative and put forward a technology that saves lives every day.

That being said, I think we can do better. Today we heard that

there was a 20 percent recall in 2006, and we've seen numbers where recalls have increased. I agree with Dr. Weisfeldt. I'm more concerned about the recall data than the MDRs. We have a million and a half of these devices out there, and I'm not surprised they're increasing in numbers of MDRs.

So I see us as having a problem, and we need to find a regulatory answer to it. The cautionary tale is the 10 years it took to get the special controls put in for stents. And with all due respect to the FDA, if we start making up a whole bunch of new systems, it troubles me that we would take longer to get it right as a 510(k) than a Class III. So that is the direction that I would be inclined toward.

The issue of slowing innovation, I think, is one we need to look at carefully, that they're innovating at the cost of dependability; that's not an advantage.

The issue of choice was raised by industry. I'm not sure that that's necessarily that big a deal. We don't necessarily need so many device companies out there if they aren't putting out a safe and effective device.

The issue of availability is important to me. These devices need to stay affordable. They need to be implemented more fully, and I think that would -- availability will be continued, as we've been reassured from the FDA, if we went to Class III. The pipeline of these devices would not be cut out.

So, fundamentally, the bottom line is I think we can do better than we've been doing, and it looks to me like the Class III designation is the

best way to do it.

DR. HIRSHFELD: Okay. Yes.

MR. BARRETT: As I step back and think about this from the highest level, I see a tradeoff of two different kinds of burdens.

Acknowledging that there are issues, as have been discussed at length, there's the burden, which is primarily on the shoulders of the Agency, of developing special controls versus the burden -- and it's really -- it's an incredible burden -- somebody shut the industry speaker's mike off --

(Laughter.)

MR. BARRETT: -- an incredible burden of preparing, submitting and then maintaining a PMA approval. And there's a lot we haven't even talked about here today, what it means to maintain an approval. And it really is rigorous.

And what strikes me is, again, you know, having rolled up my sleeves and worked on studies and prepared submissions, one of the real key components of a PMA that differentiates it from even a 510(k) with clinical is the kind of questions you're asking. What's the valid scientific evidence, the kind of clinical study? It impacts the type of submission and nobody here is really saying that -- at least from the FDA's point of view, that there needs to be randomized controlled studies and that we need to notch up the level of clinical evidence. And that's one of the real tenets of what a PMA is.

And as I am here and I'm supposed to represent the industry

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and not just the industry that brings products to this Panel, I have a real significant concern that decisions made here by this Panel could impact all the medical device industry. If every time we have a product and there are really compliance issues or quality issues, if the reaction is to move the product from Class II to Class III, I'm concerned about the precedent of what might occur there.

DR. HIRSHFELD: Thank you.

DR. LoGERFO: I was really impressed with the answer to Mr. Dubbs' question and it was mostly silence. One offer was put forward about a 510(k), if I heard correctly, it was kind of brief -- that was submitted in 2010 and that product is in Europe but it hasn't been released here yet. This had to do with the plugging into AC or to a battery current and monitoring the temperature. Now, that's a concern because failure to operate is the number two failure point of these devices. So it seems to me that it makes sense to look into these things.

And I didn't hear any documentation that the current process is holding up innovation of this product. I'd be happy to hear more on that subject, but it just didn't come forward.

Secondly, I really agree that the data are incomplete. For example, ask yourselves, how many of these devices have been deployed in the United States? Because all we've heard is this 1.5 million in the United States and Europe. So I don't know what that denominator is, and that

denominator was used in the one of the presentations here.

Clearly, we could do much better in gathering data, and if these data -- if these devices can self-report after an incident, it's almost inexplicable that we don't have very detailed data for each of these uses of the device where it failed.

And the studies -- and I agree, you're not going to get a controlled randomized trial here. But the studies, as I read them, are inconclusive, and we can debate that and I'd be glad to do that. But I think they're inconclusive because it's so hard to separate the technology from the environment, the training, and the application.

But I think, before we loosen this up and these devices begin showing up all over the country under circumstances where they could do harm, I think the current process, so far I haven't seen a strong argument to change it.

DR. HIRSHFELD: Dr. Kelly.

DR. KELLY: So it seems to me, in listening to the discussion, that people are more or less in agreement with what we need or what we might need as far as premarket inspection and post-approval studies, some kind of annual report, and what it comes down to is, is how can it be done? And it seems that although it could possibly be done with Class II special controls, that would be cumbersome, but we know it can be done with Class III premarket approval.

In addition, given how effective these devices are when they work, I'm not enormously concerned about slowing innovation because I think for now we have pretty good devices, as long as they're functional.

So I would think at this point I would be in favor of a premarket approval process.

DR. HIRSHFELD: Dr. Jeevanandam.

DR. JEEVANANDAM: I agree. I mean, I think again, you know, there's two concepts here. One is it needs to defibrillate a patient, and I think the devices we have have shown their able to do it. I mean, if innovation is things like temperature sensors, I don't know, it's not huge, I mean, unless somebody comes up with a triphasic, quadriphasic, or something else, where you can have much smaller device. You know, these small iterations, you know, it's not going to be a major concern of mine.

So in terms of innovation, I think, you know, it's not that much of a concern looking at the data. My biggest concern is that yes, you have a device, you're going to use it. What confidence do you have that it's actually going to work? And if that means that we need to have the rigors of a type III device with a PMA to make sure that they're tracked and they can be serviced and we know the denominator, then I think that's what I would favor.

DR. HIRSHFELD: Dr. Naftel.

DR. NAFTEL: So, as I think through this -- and I really appreciate all of the presentations. They helped me in my thinking a lot. I have one

issue that I really wanted to ask FDA and the Panel.

The normal process when a device is approved is, well, first we have FDA to keep things on target, and then we usually have a physician that makes a decision, and then it gets to the patient who, under today's informed consent, gets to hear the risks and the benefits. And it's not like it was 20 years ago where the informed consent says, you know, you might die, you might get an infection and all that. It's totally different today. It's probabilities and it's risk/benefit ratios, and the patient gets to be part of this decision process. Now, admittedly, the patient leans on the physician, but the patient's involved.

But we're talking about obviously a different situation. There is no informed consent. The patient never gets to hear about four different approved devices and, you know, one has different power-up rates than the other, and there's no judgment that he or she gets to make. So we're making that for them. We're doing the informed consent for the patients.

So that's my question. Does FDA consider the burden a little bit higher or the responsibility a little bit higher in this case where the patient has no voice whatsoever?

DR. HIRSHFELD: Other comments? Dr. Ohman.

DR. OHMAN: So this has been a fascinating day. I learned more about a lot of things that I knew nothing about, and I'm sitting here much better educated, as always.

So I think this sort of, as I see information being presented here, falls into sort of several different categories. On the first level, the first question I asked myself, does self-regulation work? And I see that a little bit of the processes we've had up to date with the Class III, but really under a 510(k), is that does self-regulation work or self-observation or whatever you want to call it? And I walk away thinking, maybe not. Because what I heard was we had more use of these devices -- terrific -- and we had more MDRs. I would expect it to be the other way around. We make something more, we get better at it, but I heard just the opposite.

And I'm sure I may not have got this right, but did I hear right, that the rate of MDR per units sold is a propriety number? And if that's the case, I think we're in the era of transparency. If I go to a restaurant in Washington, D.C., I get the hygiene rating. I would like to see a rating on this because the reality is that we would expect certain things at a certain level, and I was stunned to hear that this was proprietary information. And maybe I misunderstood it, so I shouldn't go down that path too far.

And then the second thing, I have to echo what my colleague Dr. Page said. You know, it's very interesting that this is an important device that saves lives. We know that. And others around this table have proven that well beyond -- the question, though, becomes if our regulatory environment is so stifling, I'm left with a question, why don't I see more AEDs when I go through the airports in Europe than I do here? And I haven't really

understood that part. Maybe there's some other issues here that I don't understand and I'd be willing to learn about that.

But I think this is a very important level. I think the self-reporting work, I haven't seen it. I think I'm going to more conservative in how I look at these devices.

DR. HIRSHFELD: Dr. Milan.

DR. MILAN: Right. So as I look at this and the big question about whether or not we should go to a Class II with special reports or whether or not we should do Class III with a PMA, it seems to me that we're trying to construct a lot of the things that are in the PMA to sort of allow us to reclassify these devices as Class II, and I guess I would have to ask what those advantages would be.

And one of the questions was whether or not it would stifle innovation. But I think that the big innovations that we would see that Dr. Jeevanandam was talking about would probably, even if the devices were Class II, require reclassification for Class III. As a major advance, a revolutionary advance, it would require additional proof of efficacy and safety. So I don't think that the innovation argument is a strong one for that.

And then I guess, you know, barring that I don't see -- I mean, I agree that the information is lacking for the actual event rates for these devices. And I think even though the MDR data has a lot of problems with it, they do highlight a signal that I think is concerning to many people on this

Panel that we've heard, and I think we should really increase the level of certainty about how these devices are performing rather than just sort of trust to what we have so far.

DR. HIRSHFELD: Yes, Mr. Simon.

MR. SIMON: I'd like to go back to my previous comment with regard to deaths. I think the industry has provided a lack of specific data, not just data. If I can't make out what the 279 is, that's a big problem.

And I also am thinking, what will reclassifying to Class III or Class II do? And the first thing I look at is will it save lives? And if I can't determine that, that to me is a lack of specific information, specific data.

And, lastly, will reclassifying to either Class II or Class III result in less manufacturing or less availability? Nothing's been shown to me that it would.

DR. HIRSHFELD: Any other comments from anybody? Okay.

MR. DUBBS: No mention has been made about the packaging, labeling, inserts, things like that. We've heard a lot of information about malfunctions and failures and reasons for failures. And I'm having trouble understanding if that's because normal day-to-day maintenance is not being performed on the devices.

I live in a community where we have a public safety fleet of vehicles, that you could call them patrolman and some EMTs. They're all equipped with AEDs, and they have a protocol where they check these very

regularly. And then I compare them to what Dr. Page is talking about, these devices on the walls in various public places.

And I just wonder what's being done to be assured that when you need to use the device, that it'll work and not because some error by the person who's responsible for having put that device where it is hasn't done something.

DR. HIRSHFELD: Any other comments? Okay, Dr. Weisfeldt.

DR. WEISFELDT: As I said once before, I find event reports not credible; as explained, that the deaths, which are obviously of great concern, are reported in a bend-over-backwards manner as required, I believe. And again, if we had the report, as suggested, that might help understand more about these deaths.

But what I know from our own experience in the PAD study as well as this data-gathering exercise a year and a half ago that we published, we are seeing very high survival rates with the use of the AEDs. Of those people who have VF and get shocked by an AED used by a bystander, 42 percent of those people walk out of the hospital alive. So I know it saves lives. I don't know that I hear the reports, but it's not convincing that these devices are having problems.

And as said before, in the randomized studies, those kind of data were gathered up, but it's very few people.

In the observational study, if we accept that there are two

million of these devices in the United States and Canada, that means, in the population that we studied of 21 million in 10 cities, there was about 100,000 devices and 220 out of 100,000 devices were used. So, you know, we could do a lot clinical research for a long time before you'd identify a safety concern by doing clinical trials.

The recalls are really concerning, but most of the recalls are based upon not patient reports of adverse events, they're based upon either self-tests, reliability or aspects of the device that are understood by manufacturers to not work.

And if special controls were strengthened to meet some of the objectives that the FDA believes would be useful and the FDA believes they have the power to do it, I don't see why we need to change from where we are in fact now, which is 510(k), which would be the Class II with the FDA strengthening the stringency on the reliability and manufacturing reporting to the FDA.

So I guess I stand with the minority and with the industry representatives.

DR. HIRSHFELD: Yes, Dr. Lange.

DR. LANGE: Again, the arguments or presentations all around were terrific, and I appreciate it, and it gave me some understanding I didn't have.

I think that these devices are different than other devices that

go through PMA and that we've had them around for 26 years, and as everybody knows, they're well proven and they're effective and they're well developed for the reason I think that they're different than other new technologies which a PMA is necessary.

I am bothered, as Magnus alluded to, to self-regulation. This issue of proprietary is beyond me. We know that these devices have the ability to record and to find out where issues are, and two-thirds of them aren't investigated by the company. And that is a problem with evaluation. If you're going to self-test and regulate, you have to look at the device, and you can't do it if it sits there. And that is an issue.

On the flip side -- and I agree with Dr. Weisfeldt, I'm in the minority as well -- is that I think that what we need to do, especially with devices that have been around for 26 years, is to develop the ability to have effective special controls. And if we can do that, then I think that this device would best benefit from being classified as Class II.

But, again, I say that recognizing that the industry isn't going to regulate this. It hasn't done it so well. It hasn't done so far. But it will take effective special controls to do that.

And I know that there are concerns that this sets a special precedent. But what I would say is I think this is a different device because it's been around for 26 years, so I don't think it falls into the usual Class III category as new devices.

DR. HIRSHFELD: Any other comments?

(No response.)

DR. HIRSHFELD: Okay. Well, hearing none, I'd like to just make a couple of observations, hopefully being somewhat synthetic from what we've heard so far.

I think everybody agrees that the public would benefit if these devices are widely available, and that for these devices to live up to their mission, they have to be reliable. I think what we've heard so far is that there are some questions about reliability, both from the MDR reports and from the recall experience. And so I think that what we need to do is -- or what FDA needs to do is to develop a mechanism for assuring that these devices are reliable.

I think the other aspect of this is that I think there's relatively uniform agreement that this is a mature technology. Although innovation is always important, innovation is not on the front burner in terms of this technology. What really is on the front burner is making sure that people have access to it and then, when they need it, that it works. So I think those are things that we should be sort of focusing our thoughts on as we listen to the FDA questions to the Panel.

And at this point we'll break for 15 minutes. So we'll reconvene at 25 of 4:00 and we'll hear the FDA Panel questions.

(Off the record.)

(On the record.)

DR. HIRSHFELD: Before we proceed with the FDA questions, I think FDA would like to make a couple of comments.

MR. SHEIN: Welcome, ladies and gentlemen, to the end of a good day's discussion and hopefully some fruitful deliberations in the hour ahead.

What I would ask you to keep in mind as you deliberate -- and there are few points that I'd like to bring back -- as I sat and listened with great interest to the industry's perspective, they offered a number of items that might be used as special controls. They offered things like standards and other guidance documents that are in place. And I would offer that many of these standards are already approved and published and are available and currently being used.

So while they are being used, they're not being used as a special control, as we've described them today for your deliberations, to Class II, should you consider to go that way. But it's something to keep in mind, that they have been in place, they have been utilized, and yet we still find ourselves in the situation where we do have an increasing number of recalls. And so they have not necessarily been effective in preventing those, and I'd ask you to be mindful of that.

Along those lines, speaking of special controls, I'd like to go back to what Dr. Luke mentioned this morning and what I mentioned earlier

as well, myself, which is there's a number of things that the Agency has recommended be included as special controls, should you decide to down-classify to Class II, things like premarket -- excuse me -- preapproval inspection, the need for annual reporting, and the need for reporting of manufacturing changes. Those are all things that could in fact be done.

But, again, as I mentioned earlier, when you take all these things together, you start to blur the line. You start to look very, very much like what is already written in the reg books under the PMA. And as we blur that line between Class II, Class III, and the 510(k) and PMA program, be mindful of that.

I don't mean to make levity of it, but if it looks like a duck and it quacks like a duck, maybe we should just, at the end of the day, call it a duck.

The last point I'd like to make is that the decision you make here today is not a permanent, etched-in-stone decision. It's a decision for the time being, until such time that it might need to be changed.

So if you were to recommend for classification Class III and call for PMAs, that doesn't mean that some of the issues we're talking today about, with respect to the MDR reporting frequency, with respect to the number of recalls that we've seen, then a couple years hence, that industry, if these things abated and it was appropriate, couldn't petition to down-classify the device back to Class II at that juncture, the same way that if you were in Class II and we had new questions of safety and effectiveness and we came to

a determination of not substantially equivalent and moved some devices into PMA.

You know, Class III is not a permanent decision by you today, and I don't want to you think, for those who are concerned, that this is a curse that can't be lifted. There is the possibility, if circumstances warranted, that we could move in that direction.

So, with that, I'll leave you to your deliberations. I look forward to listening.

DR. HIRSHFELD: Okay, thank you.

So we will now move to the FDA questions for the Panel, and I believe Dr. Tovar is going to present those.

DR. TOVAR: Question Number 1:

In determining whether AEDs should be regulated as Class II or as Class III, FDA focused its review on the ability of these devices to appropriately detect ventricular arrhythmias and deliver therapy. A malfunctioning device compromises the ability to rescue a patient.

a. Do you agree that this is the most significant safety and effectiveness issue for AEDs?

DR. HIRSHFELD: Okay, do you want us to address both parts of Question 1 initially, or do you want us to just do (a)?

DR. TOVAR: Right.

DR. HIRSHFELD: Just part (a)?

DR. B. ZUCKERMAN: You can go for both. Go for both.

DR. HIRSHFELD: Let's go for both.

DR. TOVAR: Okay, let's do the other one.

- b. Should other significant safety and effectiveness issues be included in this consideration? If so, please identify and discuss.

DR. HIRSHFELD: Okay. So I'm open for comments from the Panel. Yes, Dr. Page.

DR. PAGE: I think this is the most important issue, whether the device actually effectively resuscitates from ventricular fibrillation. In terms of other considerations, I think that maybe it's implied, but it needs to tell the difference between ventricular fibrillation or pulseless VT and other arrhythmias so it would not recommend a shock.

And, finally, with the revelation that some of these devices actually deliver the shock without a commanded push of the button, I think that needs to be considered as well.

So not only does it recognize the true arrhythmia and be able to deliver therapy, but it recognizes what isn't the true arrhythmia.

DR. HIRSHFELD: Other comments? Dr. Weisfeldt, do you have your microphone on for a reason? No, you don't, okay.

Any other Panel members have any -- Dr. Naftel.

DR. NAFTEL: So apparently everybody's up to speed on this,

but I just wanted to make sure that within the thinking is what was brought up earlier about the packaging, the instructions, and making sure that a layperson knows what to do. So it's not just that the device works but it's that the therapy works. So that's just something I want to keep in mind as we go through this.

And then it was mentioned once, and apparently it's not an issue, but is there any danger to the user, any, you know, shock danger? And I don't know, but that seems like another consideration to me.

DR. HIRSHFELD: Any other comments from the Panel members?

DR. LoGERFO: Is this with regard to both of these questions?

DR. HIRSHFELD: Yes.

DR. B. ZUCKERMAN: Yes.

DR. HIRSHFELD: Both questions.

DR. LoGERFO: Yeah, because I think it kind of goes hand in hand with that, how these devices stand up in the environment to which they're dispensed. And granted, under ideal conditions, the device, I think we all agree, when properly administered and especially by trained personnel, they work great and properly, by trained personnel. And properly maintained.

But the big question is, since some of the problems are problems that really would result in a failure if the devices are not properly

maintained in the environment, I think that's an important part of this. Not just that it works when it goes out the door, but that it works in the environment over a period of time and we can be assured that that's the case.

DR. HIRSHFELD: Other comments from other Panel members?

Yes, Dr. Slotwiner.

DR. SLOTWINER: I do think that the primary goal should be to ensure the reliability of these devices. Our primary goal is not to -- we're not expecting any new technology here in the near future. And so I think confidence from the public in these devices being reliable and making these devices available and helping the public understand them and spread them is the key. And so reliability is by far the number one concern, I think, we should have.

DR. HIRSHFELD: Any other comments from any other Panel members on this question?

(No response.)

DR. HIRSHFELD: Okay. So, Dr. Zuckerman, I think it's fair to say that the Panel agrees that safety and effectiveness are the -- safety and effectiveness, meaning a correct recognition of arrhythmias and properly operating to deliver therapy, are the principle safety issues for this device.

I think the Panel has also highlighted the fact that many of these devices are devices which are dormant for extended periods of time

before called into action, and that there are potentially important issues of whether or not these devices will remain in good operating order prior to and at the time that they're actually needed. And so these are some quality issues that need to be considered in their regulation.

DR. B. ZUCKERMAN: Okay, that's very helpful, but what do other people think about Dr. Naftel's comments that human factor studies should be an important part of the evaluation of whether this device is safe?

DR. HIRSHFELD: Okay, let's open it up to Dr. Naftel's question.

DR. LANGE: I think that goes to the issue of effectiveness, and that is, the effectiveness isn't, as Dr. LoGerfo mentioned, whether you can activate it before it goes out the door or whether it's in the field. In other words, if you've got a device but nobody knows how to use it, it's not very effective. So it goes to the field testing.

DR. HIRSHFELD: So these are issues of interface design, so somebody who doesn't understand the device, in the heat of the moment, can use it effectively and can recognize whether it's working properly.

Did you have a question, Dr. Slotwiner?

DR. SLOTWINER: I just wanted to make a comment. I have the impression that these devices, once they are out of the -- once they're sold, there's less involvement from the vendor than we have for most equipment in medical settings, and I think that gets to part of the human interface, and I think that there needs to be more participation by the vendors, once it's sold,

in both educating the public and continuing to make sure there's a mechanism for reliable function as it's been sitting on the wall for years before it's called into service.

DR. HIRSHFELD: Any other comments from the Panel?

(No response.)

DR. HIRSHFELD: Okay. So, Dr. Zuckerman, is this helpful and adequate?

DR. B. ZUCKERMAN: Very helpful.

DR. HIRSHFELD: Okay. All right, Dr. Weisfeldt has a comment.

DR. WEISFELDT: I think the point about interface is important.

As an example, I think one could advocate in this country that the device should have an option of Spanish, as well as English, as an interface issue.

So I think, yes, I think the point is well taken, and I think that the Panel should note that those kind of issues, very simple issues that may affect the efficacy of use of the device, ought to be considered.

DR. HIRSHFELD: Okay. So I think, then, we're ready for the second question.

DR. TOVAR: Question Number 2 is:

The primary sources of information that FDA reviewed to identify the risks associated with AEDS were device recalls and adverse events reported through the Medical Device Reporting system. Are there other sources of safety and effectiveness information that need to be included in

FDA's identification and evaluation of AED risks? If so, please identify and discuss.

DR. HIRSHFELD: Okay, Mr. Dubbs.

MR. DUBBS: Well, it's hard to know because we weren't presented with information, and I raised the question earlier about package inserts, packaging, identification for people to put it into use, and then periodic inspections and updates. So I'm having trouble focusing on where we would go with this question.

DR. HIRSHFELD: Okay. Other comments? Dr. Ohman.

DR. OHMAN: I was encouraged to hear a collaboration between somebody in Colorado -- I didn't get all the details -- and the FDA, of some, what I would call, registry information in this field. And obviously Dr. Weisfeldt and others have carried out such things because, generally speaking, for areas where we have little knowledge because it's sort of almost outside our arena, those types of efforts usually leads to observations that help us to focus our future research and going to innovation.

I'm not proposing that this should be carried out by the industry, but I think the idea of collecting information sort of objectively away from the medical setting that we typically collect information is very important.

DR. HIRSHFELD: Dr. Weisfeldt.

DR. WEISFELDT: I'm likened to compare the detail of what we

do in the clinical environment today with an adverse event where we have detailed deliberation, sentinel event reporting, a root cause analysis, going forward with each one of these and trying to learn from it.

And then I look at the superficiality of both the FDA's approach to these deaths and the companies', and I'd say this is just an inadequate, atypical response to the allegation that these are deaths that are related to the use of these devices.

And I don't know whether this is a regulatory issue or an inspection issue or what it is, but the superficial nature of the information we have is really quite striking compared to the change that we have done in our society about adverse events, where we take the adverse event so seriously and look at it so carefully.

DR. HIRSHFELD: Dr. Naftel.

DR. NAFTEL: So I believe with a little bit work, the MDRs could produce some good information, if they were just sorted by whether or not the report was associated with a patient itself or was it just the freestanding device.

With a little work there, a little work looking at those deaths, and if we could get where we were relatively happy with the results, and then immediately what I would like to do is split by device, because it's one thing to talk about this issue as the field, that the field's doing great, AEDs are doing great and all of that. But if I saw it per device and I could say, oh, these

rates really differ a lot, whether it's rates of recall or death or whatever, then I might get a little more uncomfortable and say, well, on the average things are great, but we've got some outliers that I wish were regulated better, regulated as maybe even removed from the market.

So I would like to see, under your question with the MDRs, to see device specific. And maybe we can't see that, but you guys could see that, and I think it'd give you a better feel for what sort of regulation needs to happen.

DR. HIRSHFELD: Yes, Dr. Zuckerman.

DR. B. ZUCKERMAN: Okay. So let me respond to Drs. Weisfeldt and Naftel.

I think what you're seeing is a classic case of a passive reporting system. For a variety of reasons, these are the best data that FDA can get at the present time. I think you're all aware of why hospital facilities sometimes are reluctant to report, et cetera, and I think from your prior experience, since I'm talking to a lot of electrophysiologists, you are aware of recent problems with lead failures, where you can have a quarter million leads implanted, that passive reporting has a lot of potential problems.

So if I were to summarize where we are, certainly the Agency will take very seriously the comments by Drs. Weisfeldt and Naftel, to look at how we're looking at MDRs to try to better coordinate with hospitals, professional societies, et cetera. But I think that passive reporting, for a

variety of reasons, usually doesn't get your where you need to go.

So then we have the suggestion, as pointed out by Dr. Ohman, that perhaps we need some sort of national AED registry. And I would like a little bit more discussion there because certainly that's something that is potentially doable with all stakeholders. I think that the quality of safety reporting could be better than where we are right now, and we really need some more discussion on that topic.

DR. HIRSHFELD: Yeah, thank you, Dr. Zuckerman.

I think actually I might propose that there be a slight rewording to Question Number 2, to also ask whether or not the Panel feels that the current information systems available at FDA are adequate or whether there are inadequacies of the information system.

And one of the things that's occurred to me in thinking about this is that the AED is an unusual -- or has unique characteristics in terms of the type of service that it performs in terms of the nature of the business transaction.

When you go to a restaurant and you order a meal, the meal is delivered and you eat it, and within an hour you know what sort of a product you've gotten.

Here, with an AED, you purchase it, you put it on the wall, and you may not find out for four years whether or not it's going to function effectively and do the job. So I think that is an indication of the fact that the

ability to tell what you have purchased and how well it works requires other kinds of monitoring systems.

Yeah, Dr. Page.

DR. PAGE: I think your analogy is apt, and if I may continue it, I'd make the analogy to a fire extinguisher which sits on the wall and you expect it to work when you need it. But God forbid you ever need it.

But getting back to the issue of fire extinguishers and the comment I made earlier today, I know where there is a fire extinguisher at this hotel, and I know that there isn't an AED, and we meet at the core of this, and arguments on both sides have argued that we really need these lifesaving devices available to us.

So that's why my radar goes up a little bit when you mention a registry, Bram, from the standpoint of whatever we do, we need to not make it harder for people to put these devices in their buildings, in public areas where there's a reasonable chance of cardiac arrest.

So my only caution if we add reporting issues to the user or the purchaser of these devices, you may get an unintended consequence, and that is less implementation. And we see a little bit of that signal with some of the other registries and concerns in terms of implantable defibrillators.

DR. HIRSHFELD: Other comments? Dr. Jeevanandam.

DR. JEEVANANDAM: I think you're perfectly correct, you know, in terms of a registry, in terms of people being reluctant to register. On the

other hand, if they register and there's a recall or there's a problem with their device, they'd know about it much faster than having to read about, or they may never know about it at all.

So I think if I was purchasing one of these for home, I'd love to have some mechanism to tell me that if there is a recall or a problem with it, that we would know about it. So you can kind of dovetail that into a registry.

And I think, without having an active registry, our understanding of these events and these recalls is just going to remain to be poor. So I think we really do need to have an active registry.

DR. HIRSHFELD: Yes, Dr. LoGerfo.

DR. LoGERFO: I'm not sure that there's anything that's holding up putting these devices in this hotel at the moment. Am I mistaken about that?

DR. HIRSHFELD: I think Dr. Page had some feelings about this.

(Laughter.)

DR. PAGE: Well, there at times are, and that's one of the issues that we talked about. There are medical-legal issues. If you're regulated and required to have a device in place, such as certain health clubs in certain states, you've got a device. If you're on an airplane, if you're in an airport, those are mandated. In other cases, it is a one-off.

One of the concerns I have is that you hear about people having issues about safety of the devices, medical-legal issues. You know, if I

have a device and it's not used correctly, am I now in trouble?

And a subtext of this meeting is there has to be a public trust in the regulations and the dependability of these devices. I don't know whether that plays into it. And one of the hopes I have in terms of this meeting and possibly better oversight and higher confidence in the safety and effectiveness of these devices is people will be less reluctant to put AEDs where they should be, such as major public buildings.

DR. LoGERFO: Excuse me, but I still haven't heard anything, as far as FDA regulations are concerned, that's impairing the sale of these devices at the moment.

And I would make just one point about the fire extinguisher. They're inspected a couple times a year, if not more often. So it's a different situation. If they weren't inspected and you picked it up and it didn't work, that's sort of what we've got now. The fire extinguisher might be there for four years and nobody's checked it.

So I think we can do better, and the idea of a registry, if we can get surgeons from many hospitals together to participate in a registry where other people come to your hospital, make sure your data is valid and so forth, so that you can participate in a regional or a national registry -- because I bring that up because surgeons are very sensitive about their results. And I don't see why we can't do that with an industry.

If we did it, if we made this transition so that there was some

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system like that, it would open up all sorts of things, as you suggest, where you could deliver innovation, you could be confident in a reporting system, and that would really advance this more than anything else. But I don't see anything in the current regulations that's holding up the process.

DR. HIRSHFELD: Yes.

MR. BARRETT: Just to draw a distinction between registries and device tracking, at least to me and, I think, to the companies, from what we've heard earlier, they're two different things. And my understanding is that, at least from the two companies that presented today, that they do track their devices, that they do keep information about where the devices are shipped, and if there were a need for a recall or for information to be sent out, that there is a mechanism to send that kind of information out; as opposed to a registry where we might be gathering additional information about the use of that or other things.

DR. HIRSHFELD: Yes, Dr. Lange.

DR. LANGE: I'm mystified by the fact that if we know where it is and it's recalled, we can replace it, but if something goes wrong with it, we don't know why. I mean, we just don't know why. They didn't send it in, and it's like people said, I have a defibrillator that doesn't work and I'm going to keep it to myself and not share it with anybody. That's mystifying to me.

But, Bram, to your point. It has to be an active reporting. It cannot be passive. We can get more or additional information, as David

suggested, from the reports we have, and we ought to drill down. But it has to be an active reporting system to be effective.

DR. HIRSHFELD: Dr. Slotwiner.

DR. SLOTWINER: One lesson we learned from the implantable leads is the product performance reports. Perhaps, you know, a statistically valid subset of devices could be tracked randomly. Sold devices could be tracked prospectively and, you know, not instead of a registry but another way to pick up infrequent problems prospectively.

DR. HIRSHFELD: Okay, other comments on Question Number 2?

(No response.)

DR. HIRSHFELD: Okay. Well, Dr. Zuckerman, I think that if I can summarize what the Panel stated, I think there's considerable feeling in the Panel that the current passive device reporting system and the recall tabulation, while providing signals about issues and potential problems, probably is inadequate to adequately track the performance of these devices, and that problem is compounded by the fact that the devices -- there's frequently a long interval between the sale and installation of the device and the actual use of the device.

In addition, there probably, on many occasions, are ambiguities as to whether or not an adverse event was actually a device failure or not. So I think the Panel clearly feels that FDA would benefit by better information

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about long-term device performance.

DR. B. ZUCKERMAN: Okay, thank you, that's quite helpful.

DR. HIRSHFELD: All right, Question 3.

DR. TOVAR: As part of its preliminary recommendation concerning the regulatory classification of AEDs, FDA identified several regulatory controls (e.g., preapproval inspection) as resources for consideration. Are you aware of any other regulatory measures that would be useful to FDA in mitigating the risks associated with AEDs? If so, please identify and discuss.

DR. HIRSHFELD: Dr. Lange.

DR. LANGE: Sorry. Four things. One is annual reporting by the company, two is a classification of the MDR standardized reporting, the third would be reporting of changes in manufacturing facilities, the fourth would be review of significant manufacturing changes, and the fifth would be standardization and interpretation of data and recall determinations and failure rates.

DR. HIRSHFELD: Other comments? Dr. Ohman.

DR. OHMAN: Yeah, I would like to add what Dr. Weisfeldt said earlier to that list, maybe a root cause analysis of every death associated with a device, sort of just like we would do in a hospital setting.

DR. HIRSHFELD: Other comments? Dr. Weisfeldt.

DR. WEISFELDT: I would just raise the question as to whether,

in a device that is so infrequently used in a sense of registry, testing, so forth, whether there is really a role of routine testing by an independent body. CRI does it as they see fit, I believe, currently, just buying devices on the market and testing them and then writing them up.

I'm not sure that this isn't one of the rare circumstances where required oversight by a neutral body of software, the hardware, the construction of the device is not warranted in the public interest.

DR. HIRSHFELD: Okay, Mike, can you clarify for me? I'm not sure whether you're advocating that there be a system in place where an independent party goes around and actually surveys individual devices on the wall and performs -- sort of part of the process of owning an AED is that you would contract for a service that would service and inspect it. Is that what you were referring to or --

DR. WEISFELDT: My own thought was that an average device that is ready to be sold would be shipped to an independent agency that would test it initially and over time, in a pretty serious way.

DR. HIRSHFELD: So it would be tested on installation.

DR. WEISFELDT: Yeah.

DR. HIRSHFELD: But are you advocating that there would be an ongoing surveillance of that device performed by an expert who would check it?

DR. WEISFELDT: Well, that's certainly one of the things that the

company or agency, or whoever would be doing it, could do or decide to do, is to keep that tested device or to keep a tested device over a period time to see that it doesn't deteriorate in terms of its function.

And it is a very unusual type of product that we're talking about here. Although it has the self-check mechanism, we're all concerned that the self-check mechanism is not actually sufficient to tell you about the reliability. And the problem is that the reliability is very rarely testable or identifiable in the real world because only .02 percent of the AEDs are ever used on a person. It's not like an implantable defibrillator, where 20 percent of the people use it. Here it's very, very few times that an actual device is actually used on a patient.

So one, I think, could advocate for a neutral party looking at the quality of the way device is fabricated and averaged.

DR. HIRSHFELD: Yeah, Dr. Jeevanandam.

DR. JEEVANANDAM: I also think it's -- you know, we kind of keep coming back to this number of 66 percent of these devices that have had MDRs were never really evaluated, and I'm wondering if there's a mechanism that could be put in place.

If one of these doesn't go through a self-check, you know, is the company obligated to send them a unit before they send the other one back? I mean, there was a comment made. You know, they wouldn't want to send a unit back because they wouldn't want to be left without a unit. But I don't

understand why they would keep a unit that may not work.

So that doesn't seem to -- you know, if I had the unit, I certainly wouldn't want one that didn't work. You want to try to exchange it. So maybe the companies -- or something needs to be mandated so they would send a unit so that that area wouldn't be without a unit and then they could just send that other one back so it can actually be analyzed to figure out what is going wrong with those devices.

DR. HIRSHFELD: Yeah, Dr. Naftel.

DR. NAFTEL: So I think we're talking around a key issue, and everybody maybe understands it, but I'm just coming along. There's two different things we can study. One is the device and how is it doing and is it holding up, can it still maintain a charge, and all of that.

And then the second thing is how does the device work with a human? And I had always thought MDRs were directed towards humans who had devices, and I guess I'm a little surprised that some of these things where a human is not even involved are reported as MDRs. So I'm a little surprised.

Then, when we talk about registries, you know, I'm thinking -- because I love registries, I thinking, what's the unit of measurement? Is it a human being that, you know, had this device used, or is it the device? And maybe we want both.

But I'm starting to think more and more, as we talk about risk and bad things happening and all of that, we need to say, are we talking

about the device used on the human or are we talking about what's going with the device on a wall? And I think we want to know both.

But, you know, we need to keep that thinking clear. It's two totally different things, totally related but totally different things. We could have a great registry on 500 devices that never even got in the human or got on the human. And is that what we want?

DR. HIRSHFELD: Okay, Mr. Barrett, I want to call you in a moment, but I'd like you to consider this issue. I wonder whether one of the issues that we're looking at is that the business model for this device really has its own unique characteristics, and if you take the one extreme that we mentioned before, the restaurant meal, where there's a transaction and the product is used and it's done, the other extreme would be the implantable electrophysiologic device, where the manufacturer of the device has an ongoing relationship with the patient and the implanter because they're responsible for a device that is continually functioning.

This is somewhere in between. But it seems to me that the relationship of the manufacturer to the customer and the public is not just that they deliver the device in a box and it worked when it left the factory, but they're actually providing a service, which is an ongoing service, which is the availability of defibrillation when needed whenever down the road.

So it's sort of an intermediate between those two extremes, and I think that has regulatory implications because that says something

about what sort of performance standards and monitoring are necessary to make sure that these devices are living up to their responsibility to the customer and the public.

And I hope I didn't derail your comment that you were going to make, but I'd be interested in your thoughts on that particular aspect of this.

MR. BARRETT: I don't feel derailed. I don't know this field very well, and I don't work in this field. I work in electrophysiology and atrial fibrillation.

To me, you know, a big part of what we didn't have time to review today, and it's been brought up already, are what are the things in the labeling that the manufacturer is specifically saying? What are they warranting? What use life are they recommending? What service routine are they recommending?

And then beyond that -- and I know I've worked for companies where we may have stated use-life, but we want to be a good company, and if something is misused or beyond life, we listen to the customer complaint and we'll decide and handle it. It may include a replacement.

So I can't comment in particular about the business model and how long the obligation of the manufacturer extends beyond the date of shipment, except to say that I'm sure that the FDA, in the submissions, is looking at the labeling and looking at some sort of reasonable life and making sure there is data to show that, you know, with a certain statistical profile,

the device is going to work over the life, given that the labeling and the service recommendations and so on, are followed.

And a very minor point that I wanted to make. I think two conversations from earlier today got mixed. We were talking about devices coming back from a recall and why we ship a device before we send one back.

It's quite possible and I think common that you may recall a big lot because one failed or you suspect they all might be at risk. It doesn't mean that all of those devices aren't functioning or even that any of them aren't functioning.

And that's why a manufacturer may send a device out and then wait, you know, for the one to come back, as opposed to the malfunction, when you know it isn't working, so let's not wait, let's send it back. I think there were two different conversations there.

DR. B. ZUCKERMAN: Okay, but Dr. Weisfeldt is suggesting a fundamental paradigm shift, as elaborated on by Dr. Hirshfeld, where there's more responsibility taken by the manufacturer, or whoever, after the device is bought. And certainly the way that we might handle that is in labeling. That would be our regulatory control, as you point out, where we really specify that, in addition to relying on internal device self-checks, there's a need for more active engagement with ECRI or whoever.

I think this is a really important point. Given our lack of data for this field, the Agency will need to consider this important paradigm shift

as well as really reevaluating the label as to what we know, what we don't know, and trying to truthfully state it.

Oscar, do you want to say anything else about what the label currently says in general for this class of devices?

DR. TOVAR: Yes, the labeling actually is directed to the user. If it is a minimally trained user or even for a layperson, the label is designed by the manufacturer and evaluated by the FDA so that we are -- we have some reassurance, we have reassurance that the device is going to be used safely and effectively.

Actually, I heard a question previously in regard to human factors. We do review these devices by human factors experts, in terms of the design of the device, in terms of the labeling, in terms of packaging. That was actually one of the important features and one of the important issues that we considered during the over-the-counter devices. That would be for AEDs for public access defibrillation.

For professional use, the label is directed on how this device should be maintained, how this device should be checked by the personnel in every shift in the hospital, for biomedical engineers and so on. It would be specific and try to address all of these specific issues from the device, to provide assurance of the safety and effectiveness.

MR. BARRETT: Yeah, I've worked with a lot of different pieces of capital equipment, and I was just trying to think of a precedent, and I can't

think of one. I mean, usually you say this thing's going to be good for a year or so on and it needs routine service, and even devices that are built in the hospitals that are expected to last for years and years and years.

At a certain point there's a transaction that occurs. Somebody buys and they now own it, and they assume a certain amount of responsibility for the maintenance and service of it, as opposed to the person who manufactured and sold it to them.

I mean, maybe the Agency is in a better position to say, at least outside of implantables, if there's any kind of precedent for that, but I couldn't think of one.

DR. HIRSHFELD: Other comments? Yes.

DR. LoGERFO: You know, I was thinking about you buy a new car and you have to take it in for service. If you don't do it, the warranty becomes invalid and things like that. So there are sort of models, but not quite exactly. This is more complicated.

But the people from industry, hearing this discussion and knowing what information we would like, couldn't there be some innovation that would make this easier?

For example, I'm thinking you could plug these things into a telephone line and once it's used -- it wouldn't have to always be plugged into a telephone line. But once it's used, you plug it in and it reports back exactly what happened. Or you could even do maintenance that way.

But I think if people know there's a problem here -- and we all seem to be honing in on the same thing, to put together some proposals to solve this.

DR. HIRSHFELD: Other comments?

(No response.)

DR. HIRSHFELD: Okay. Well, Dr. Zuckerman, I think if I can summarize this, I would say that the Panel feels that certainly additional regulatory controls are needed. I think the Panel expressed a concern that manufacturing may not be adequately regulated, and there was an expression that more inspection and regulation of the manufacturing processes would be beneficial.

There was a number of expressions of feelings that the long-term monitoring of the performance of the device is currently inadequate, potentially leading to problems of device failure in the field because of inadequate monitoring and inadequate maintenance.

And so I think these are the two areas where, as far as maintenance as an operational capability is concerned, that the Panel feels it could be addressed.

DR. B. ZUCKERMAN: Okay, thank you.

DR. HIRSHFELD: Okay. All right, next question.

DR. TOVAR: And the last question is:

Please provide your overall recommendation for the

classification for AEDs from the options listed below:

- Class I
- Class II
- Class III

DR. HIRSHFELD: Okay. So far I've heard some people who appear to be in the Class II camp and some people who appear to be in the Class III camp. So perhaps what we should do is hear first from people who are advocating for Class II and then we'll hear from people who are advocating for Class III. There were people who were advocating for Class II.

DR. LANGE: Yeah, it looks like everybody's looking towards us.  
(Laughter.)

DR. HIRSHFELD: Yeah.

DR. LANGE: Why would that be, Dr. Weisfeldt?

For the reasons we mentioned, is that it's a technology that's been around for 26 years, and its effectiveness, when you have a safe and reliable device, is beyond question. And really what we need is special controls to ensure that the limitations we've noted today are addressed.

DR. WEISFELDT: Yeah. I mean, I think this is a purely American device. It's a product of creativity and ingenuity and a willingness of the FDA to work with medical people and organizations to train non-physician providers to do this lifesaving procedure of defibrillation. And I think, by and large, we have been well served by the 510(k) process.

If you go to a Class III, you're not going to get a big randomized clinical trial with lots of data like you are with a pharmaceutical device or even an implantable defibrillator because the frequency of use to get in the PAD study, there were 30 resuscitations in the intervention arm and 15 in the control arm after 3 years and 1,000 sites. This is a rare event.

By being Class III, you're not going to produce safety and efficacy data that is typical of drugs or other devices that are in more frequent use. So it really is the other features of the Class III that, by and large, can be implemented with a little bit of effort in Class II, but yet not put the intense onus of establishing safety and efficacy which is associated with Class III.

So, therefore, I think with enhanced controls and enhanced efforts at safety and some clever ideas for how we really do identify malfunctions of the device and the safety of the device, I think we're better served by Class II.

DR. HIRSHFELD: Other comments? Yes, Mr. Barrett, you've lived Class III a lot, so I'm sure you'd give us some thoughts.

MR. BARRETT: Well, I can echo the comments of Dr. Lange and Dr. Weisfeldt.

I think the Agency has perceived a problem and wants to address the problem. I believe that if the process for developing special controls were easier, we might be having a different discussion at that

meeting and talking about developing the special controls. I hear what you're saying, and I understand that it's an onerous process.

But to me, again, at the end of the day, the hallmark of Class III is not only the definition of what's a Class III device -- and I think these devices meet the definition of Class II with special controls. I think the industry presenters made a good case there. To me, the hallmark is this sort of valid scientific evidence, this pivotal clinical study which, as we understand it, is not going to be part of this PMA submission. And in my mind that is really a big distinction between the 510(k) submissions and the PMA submissions.

DR. HIRSHFELD: All right, other comments? Some of the people who would be advocating for Class III could, if they have thoughts.

DR. B. ZUCKERMAN: Okay, if we don't have volunteers, we're just going to go around the table because this is the critical comment that the Agency is really asking.

DR. HIRSHFELD: You're stealing my thunder, Bram.

(Laughter.)

DR. HIRSHFELD: Okay. Yeah, Dr. Kelly.

DR. KELLY: I think this is probably reiterating what I said before, but I don't think any of us think that making this Class III with a PMA is going to give us new safety and efficacy data. But it sounds like Class II with special controls is just too cumbersome to work at this stage, and we

know that Class III with PMA works.

So for that reason, for practical reasons, I would think Class III with PMA would be the way to go.

DR. HIRSHFELD: Okay, Dr. Page.

DR. PAGE: I agree with Dr. Kelly. It always gives me pause to disagree with Dr. Weisfeldt, who's probably done more for the world of resuscitation than the rest of us put together over the last several decades. And I think part of this is semantics, at least to the panelists. I realize it's far from semantics to others who have spoken today.

My sense is the Panel agrees there's been a problem and it needs to be addressed. I see the best way to address it is through the PMA process because basically the 510(k) has not been successful even when there was a clear signal in 2006. So I think further regulation is mandatory.

But, nevertheless, we all need to keep in mind, these devices are excellent. They save lives. FDA is promising that if we go the Class III direction, they won't keep these devices from being available. And my hope is, as we develop increased public trust, we'll develop greater implementation of public access defibrillation.

DR. HIRSHFELD: Okay, Dr. Milan.

DR. MILAN: So I agree with Dr. Page.

And I also want to sort of reiterate one of the points that we made before, which is that it seems like, to make it Class II with all these

special controls, this really almost creates a parallel track that looks, at least to my eyes, to a large extent very similar to a PMA, and I'm sort of sensitive to the argument that it may blur the distinction between Class II and Class III to have a Class II with so many special controls that it starts to look like a PMA approval process.

DR. HIRSHFELD: Okay. Dr. Karasik, do you want to comment?

DR. KARASIK: So I am in agreement with my colleagues on the Class III choice.

I still have some hesitation because I'm a little troubled by the fact that defibrillators that we use in the hospital are in a Class II. But I decided that the way I'm going to think about this is that AEDs are lifesaving devices that we are trying to push into the public domain and make them extraordinarily simple and useful at every level of education.

And I think what you pointed out, we have taken away the patient consent and we've put the onus on us to make sure that this care that we're offering these people is truly effective.

And I agree, we're not going to get better safety data, but -- effectiveness data, but that we need to do everything in our power to make sure that these are safe and efficacious for the patient. And so I think we have to take the higher road and be more stringent in our controls on these devices.

DR. HIRSHFELD: Dr. Jeevanandam.

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DR. JEEVANANDAM: I agree. I think the only way we're going to get some good, active accumulation of data on these patients is to make them Class III. And in terms of, you know, getting them approved for safety and efficacy, I don't think -- you know, the FDA's not mandating that all of these have to be randomized clinical trials.

So I don't think it's going to necessarily slow down the innovation. And I think if we can track them better so we understand their deficiencies and when they failed and why they fail, then we can solve -- we can improve that situation. I think, then, we should classify them as Class III.

DR. HIRSHFELD: Dr. Naftel.

DR. NAFTEL: So I agree totally with the last three speakers, that I would vote for Class III just because I like that distinction between II and III. And I agree that if you had II with all the special controls, you're blurring the line.

The one comment I wanted to make is, just about everybody has said we all agree that these devices work. Well, to me that's a dangerous line of thinking because it implies that the next one from a brand-new company, of course, works and I'm not willing to make that leap at all.

To me each device is its own device, and it may be in a class, but I don't automatically give it a pass because it's an AED. It's a new device. I have no idea if a new company with a new AED will work. So I'm just objecting a little bit to that line of thinking.

DR. HIRSHFELD: Dr. Slotwiner.

DR. SLOTWINER: Yeah, I agree with the Class III recommendation. I don't think the 510(k) has been satisfactory, but I'm not sure the Class III alone will be, and I think that it's going to be imperative for industry and the FDA to work together to figure out a way to monitor these devices and continue adequate function and education after they're sold.

I'm not convinced that the increased regulation will significantly impair the availability. And I hope there'll be more, at least.

DR. HIRSHFELD: Dr. Ohman.

DR. OHMAN: Well, I would vote for a Class III, a recommendation of Class III classification of this device.

I think what I've heard is very compelling evidence for both sides, but I do believe that, as Dr. Weisfeldt said a few minutes ago, actually the United States or North America has led the way in AED technology. And why can't we then lead the way in understanding the functionality of AEDs and the performance? I see this as a real opportunity for us to lead the way, recognizing that AEDs are not used a whole lot in the rest of the world, although that is changing.

I do think that there is a message in all of this, and I think the biggest concern for me in today's environment is transparency. I think there is data out there for transparency to use, and I'm hoping that by being transparent on functionality and reporting systems, that we can actually get

to that level of comfort that the public deserves, namely a functional device 100 percent of the time. I know it can't probably happen, but 100 percent of the time, that's really what I'd like to see.

DR. HIRSHFELD: Okay. So Drs. Kelly, Weisfeldt, and Lange have already weighed in.

So Dr. LoGerfo, do you have any other comments?

DR. LoGERFO: Well, I favor going to the Class III level. I don't think it will affect the in-hospital devices very much because hospital reporting systems are so strong already. I don't think it's going to be any more of a demand on the reporting system.

I think the point about informed consent is really important. A person who has an arrest is totally dependent that that device works at that time. The reporting system could be drastically improved, and we need some motivation to do that.

I think the concern of going to Class II, in terms of new devices, is a very real one at that time, when we have these concerns about the deployment of the current devices.

So considering all of these items, I think that it's better to have this in Class III.

And for industry having heard these concerns, they've been pretty clearly outlined here. We want to be sure the device works when the time has come for it to be used, and we want a report afterwards as to how it

worked. And there are probably a lot of ways to improve those two things, but we haven't gotten there yet. So I'd put it in Class III.

DR. HIRSHFELD: And Mr. Dubbs and Mr. Simon, our Consumer representatives. Consumer and patient.

MR. DUBBS: I think it should be Class III for several reasons. First of all, it's a lifesaving device, it's high risk, and if we look at the definitions in the regulations, I think it falls clearly under Class III.

We heard from the industry representatives that in terms of examples of innovation being stifled, that they could not come up with any significant description.

And developing special considerations if it were to go into Class II, I think the difficulty, the long-term process, the burdensomeness would not alleviate costs or information and that a PMA would be probably less intrusive.

DR. HIRSHFELD: And Mr. Simon.

MR. SIMON: Being a non-voting member, I actually had the luxury of being able to vacillate, so I'm going to take that luxury.

For all the reasons mentioned for reclassification to III, I would agree. I also would agree with Dr. Weisfeldt, Lange, and Mr. Barrett with regard to II.

What, I guess, makes my determination with regard to III over II is that I don't think the industry did their job. Had they done their

homework, had done their job over the last three to five years, we may not even be here. The answers would've been written out, and it would've been a foregone conclusion one way or the other, in my estimation. Therefore, if they didn't do their job, I think you have to go with III.

DR. HIRSHFELD: Thank you. So I appreciate all the Panel members' input, and I'm going to see if I can try to synthesize this into something coherent.

I think there's a sense on the Panel that there's an advocacy for Class II, and the principal rationale behind Class II is that this is felt to be a relatively mature technology and really not subject to clinical questions about efficacy that need to be asked. And so, therefore, the type of pivotal trials that are ordinarily associated with Class III PMAs are really not as relevant to this class of devices.

That being said, given that there are a number of signals that raise questions about quality and reliability, that's led to the concept of possibly Class II with special controls. Looking at this, it seems to me that what is being proposed in the people who are advocating for Class II with special controls is really sort of a Class II point 75, and so it's something that is getting close to most of the provisions that go with Class III.

I think that the members of the Panel who are advocating for Class III are advocating for Class III predominantly because of the lifesaving importance of these devices and the real importance of assurance of the

long-term reliability of these devices in the field.

And so it's possible that maybe there can be -- but on the other hand, as has been pointed out by Mr. Barrett, some of the effort involved in preparing a Class III PMA is substantial and might in some senses be considered to be sort of redundant and not productive work.

So it's possible that maybe what the Panel is really suggesting to the Agency is that what would be optimal would be sort of a Class III lite, which would be a system in which FDA was satisfied that it had satisfactory monitoring and controls over manufacturing and product quality and was also satisfied that it had sufficient ongoing product surveillance and adequate ongoing information about performance of the products in the field, so that it could appropriately assure the public that these devices are performing in the field as intended and as designed, but yet not view these -- have to view these devices from a regulatory fashion as a new device that needs to have a clinical rationale established through clinical trials.

So I think that's the way I kind of synthesize what everybody said this afternoon. I'd be interested to hear from members of the Panel if they agreed or disagree with the way I'm putting this together.

Dr. Lange.

DR. LANGE: Just a thumbs up. The only other additional information we got is it's good to sit next to a sixth grader, in my view.

(Laughter.)

DR. HIRSHFELD: All right. So, Dr. Zuckerman, is this helpful to the Agency?

DR. B. ZUCKERMAN: That was a very helpful summary, and I want to thank everyone for an extremely productive day and discussion today.

DR. HIRSHFELD: And, similarly, I'd like to thank the Panel. I think we've been blessed today with a very able and very resourceful Panel who clearly put a lot of effort into preparation for today's meeting and understanding these issues and, I think, raised a number of very important points very nicely and kept the discussion on a high level.

And I'd like to thank the FDA for all the effort they put into organizing this information.

And I'd like to thank the industry representatives who, you know, were very effective in helping us understand how this issue looks from the industry perspective.

So with that, I think we can adjourn. Thank you.

(Whereupon, at 4:44 p.m., the meeting was adjourned.)

CERTIFICATE

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

CIRCULATORY SYSTEM DEVICES PANEL

January 25, 2011

Gaithersburg, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

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