Summary from the Circulatory System Devices Panel Meeting – January 25, 2011

Summary
A meeting of the Circulatory System Devices Panel was held on January 25, 2011. The Panel discussed and made recommendations regarding the regulatory classification of Automated External Defibrillators (AEDs) to either reconfirm to class III (subject to premarket approval application) or reclassify to class II (subject to premarket notification), as directed by section 515(i) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C 360e(i)).

Device Description
An automated external defibrillator (AED) is a device with a rhythm recognition detection system that delivers an electrical shock to treat ventricular fibrillation or pulseless ventricular tachycardia. The delivery of this therapy can be either fully automatic or semiautomatic. The difference being that Semiautomatic Defibrillators analyze the cardiac rhythm and if the arrhythmia detection algorithm classifies the rhythm as shockable, then the device prompts the rescuer to press a button to deliver a defibrillation shock; whereas, Fully Automatic Defibrillators deliver a defibrillation shock if commanded by the device software without user intervention. Fully Automatic Defibrillators are used by trained users in homes, public access defibrillation (PAD) programs, Emergency Medical Systems and hospitals. Semiautomatic Defibrillators might be stand alone or incorporated into more complex devices that include monitoring capabilities (ECG, SpO2, NIBP, EtCO2, etc), and might allow for both manual defibrillation and automated defibrillation. These monitor/defibrillators are used by professionals mostly in Emergency Medical Systems and hospitals.

Indications for Use
AEDs are indicated for the termination of 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.

FDA Presentations:
FDA opened the meeting with Cara Krulewitch's extensive overview of the FDA's Post Approval Study (PAS) program, including the definition of the Agency's 522-mandate for Class II post approval issues. Next Marjorie Shulman, from Program Operations Staff, described the Agency's Device Classification and Reclassification strategies, including describing the different classes of devices, classifying pre and post-amendment devices and gave a thorough overview of the reclassification process.

Dr. Oscar Tovar, the lead reviewer for the 515(i) project for AED devices, outlined the regulatory history of AEDs; summarized the existing classification process; provided a comparison between 510(k)s and PMAs; described clinical and animal data studies involved in the premarket review process; and gave a brief overview of the Human Factors, engineering and software characteristics reviewed by the Agency. Roberta Sullivan, from the Office of Surveillance and Biometrics, gave an overview of the Agency's medical device reporting system

including adverse event report reviews (MDRs) described in 21CFR 803. She explained the MAUDE database and the frequency and types of MDRs related to AED devices reviewed and analyzed by the Agency. These reports were broken down into the most common AED device problems, including: error messages, failure to power up and component failure. Bradley Quinn, from the Office of Compliance (OC), gave a detailed postmarket data review and analysis of AED device issues, including: recalls, inspections and regulatory actions. Mr. Quinn touched on the fact that there have been 68 recalls, including 17 Class I, some of which were the basis for nine warning letters issued to AED manufactures since 2005. Mr Quinn also noted that OC has discovered multiple quality assurance problems through FDA inspections. Dr. Tovar indicated that based on the data reviewed and the current regulatory structure of 510(k) and PMAs; the preliminary recommendation of the review team was that AEDs be classified as Class III medical devices subject to PMAs. John Sapirstein, M.D., a Clinical Reviewer for ODE, gave an alternative perspective in favor of down classification of AEDs to class II with special controls. Dr. Sapirstein indicated that the Agency's PMA paradigm may slow the process of commercial availability of these devices. Dr. Sapirstein stated the potential benefits of Class II AEDs, stating that this would be the least burdensome approach for industry. Finally, Dr. Tovar wrapped up the FDA presentation by discussing both, reclassification of AEDs into class II, and reconfirmation of AEDs as class III. Dr. Tovar noted measures believed by the review team to be necessary to appropriately regulate these devices in addition to the currently provided engineering, software, human factors, animal studies, and clinical studies information. Specifically, the review team proposed the need for

- Premarket review of manufacturing information
- Pre-approval inspections
- Review of changes in manufacturing facility location where finished devices are manufactured
- Postmarket review of significant manufacturing changes to ensure that the changes are adequately evaluated and tested prior to implementation
- Annual reporting of device performance

Dr Tovar noted that were all of these to be incorporated into special controls under 510(k) it would substantially duplicate the requirements of the current PMA regulation and that the creation of a parallel regulatory paradigm would significantly blur the distinction of the regulatory classifications. Hence, the team's recommendation was to regulate AEDs under Class III.

Panel Deliberations:

The panel discussed the different types of AEDs available on the market, distinguishing between manual defibrillators and automated external defibrillators.

The Panel discussed the number or recalls and device failures compared to the death rates of patients involved. A point was brought up that annual reports could be a great tool to capture signals of possible problems with a PMA application; this would be hard to track in the 510(k) process due to the changing 510(k) numbers for differing product models/lines.

Another problem noted by the Panel is that the quality issues in these devices are critical due the fact that these devices will sit on the wall for months/years without being used; the panel stated that there should be a failsafe mechanism that will ensure these devices are in good working order when needed.

There is a disconnect between device reporting and follow up reports, where 66.5% of reports did not have a manufacturer evaluation.

The panel agreed that more information is needed in the MDRs to establish whether the device was responsible for the injuries and deaths reported. It was inferred that the manufacturers were not doing their due diligence in disseminating their AED reports to the FDA.

The panel agreed that these devices are very important life saving devices, however, there, seems to be a reliability issue. This is a mature technology and it should be more readily available and reliable.

The panel discussed the issues created by down-classifying of AEDs by setting a precedent for other devices following suit with the new special controls established for the class II AEDs.

Open Public Hearing:

Paula Lank, Vice President of Regulatory and Clinical Affairs at Physio-Control – Ms. Lank provided data to support the down-classification of AEDs into class II with special controls, stating that the PMA-route is too restrictive and would not allow for the rapidly changing AED technology and innovation, further she supported the notion of an annual reporting requirement would help to gather more data lacking in the MDRs received by the Agency. Paula pointed out that there is valid scientific evidence supporting the safe and effective use of AEDs and provided a list of literature to support this notion. Currently 97% of the MDRs were malfunctions that were self detected by the AEDs themselves.

Diana Zuckerman, PhD., National Research Center for Women & Families and Cancer Prevention and Treatment Fund – Dr. Zuckerman supported the reconfirmation to class III for AEDs, citing that survival depends on "rapid sequence of rescue events including a successful shock from AEDs." The malfunction of an AED can lead to death and this is a risk that cannot be taken by down-classifying AEDs. PMAs will actually improve the quality of AEDs due to the stringent process and the additional safeguards. Even with the PMA process intact for AEDs we still have seen numerous recalls of AEDs that continue to rise, down-classifying AEDs will only multiply these recalls.

Vernin Trimble, Senior Director Quality and Regulatory Affairs, Philips Medical - Philips submitted a reclassification petition to FDA in 2009 in response to the 515(i) order. Mr. Trimble described the history of AEDs and pointed out that the technology today far exceeds the first AED machine cleared in 1984. MDR issues are not readily apparent within current literature; the MDR reporting system is not reliable and is open to interpretation by the manufacturer and FDA.

Paul Smolenski, , Senior Director Quality and Regulatory Affairs, Philips Medical - described the regulations of down-classification of special controls, citing AED standards and testing standards, risk assessment standards are well understood for AEDs and would be more appropriate in 510(k) pathway using special controls.

Dr. Michael Carome, Deputy Director, Health Research Group, Public Citizen - 68 Class I recalls since 2004, resulting in numerous deaths. Dr. Carome advocates to the reconfirmation of AEDs into class III, due to the number of recent recalls, MDRs and deaths related to AED malfunctions.

David Belkin, Esq. - Sudden Cardiac Arrest foundation – Mr. Belkin is a survivor of a sudden cardiac arrest due to the use of an AED device. There are over 295,000 cases of out-of-hospital sudden cardiac arrest. Despite the small fraction of malfunctions that occur in AEDs, they are not known to cause more damage in patients. AEDs are life saving devices and should be down-classified, in order to be made more readily available to the public.

Panel Deliberations/FDA Questions:

In the afternoon, the Panel was given the opportunity to address FDA's questions. In general, the Panel offered the following recommendations in response to the FDA questions:

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.

Do you agree that this is the most significant safety and effectiveness issue for AEDs? The Panel agreed that the reliability of the AEDs is a major concern, as we are not expecting any new technology reliability is the number one concern.

Should other significant safety and effectiveness issues be included in this consideration? If so, please identify and discuss. The vendor should be involved in the maintenance of the devices and interface with the public in the form of training. Another consideration is that the IFU should be written in Spanish in addition to English.

2. 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 (MDR) 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. The MDRs system is somewhat inadequate to make any scientific determinations concerning these devices, there is missing data and no denominator. The MDRs should be revisited and re-worked to be able to catch pertinent information, i.e. split the MDRs by device, patient, outcome etc.

Registry information should be established to collect more data. An active reporting registry would help with recalls and would help to maintain the quality and confidence of the data collected. Sold devices could be tracked prospectively, and long term device performance would be captured.

3. 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.

- Annual reporting,
- Classification of MDRs,
- Review of significant manufacturing/software changes,
- Analysis of MDR deaths
- Automatic device reporting
- Long term monitoring of the devices, by the manufacturer
- If a unit self checks and does not work, a new unit must be sent out immediately and the old one analyzed
- Root cause analysis for every death reported

4. Please provide your overall recommendation for the classification for AEDs from the options listed below:

Class I
Class II
Class III

The panel was split between Class II and Class III. A small minority group recommended class II. This group argued that there is hard evidence showing the safety and effectiveness of the device over a long period of time, they argued that a Class III placement, would not and has not produced a robust study needed to show independently, its safety and effectiveness. They argued that Class II with special controls can establish safety and effectiveness and will help stimulate innovation and ultimately bring devices to market in a quicker less burdensome fashion.

A significant majority group argued that the AED is a lifesaving device and therefore belongs in Class III. There already exists (MDRs/recalls) a perceived problem with the device in Class III, and a Class II placement with special controls will be too difficult and contrived to be a successful short-term answer. The panel indicated that the industry could not present a specific example where regulation stifled innovation and there is no evidence that PMAs would decrease availability. The Class III mandates the device to stand on its own to prove its safety and effectiveness. The Class II with special controls will blur the lines between the two regulatory classes and essentially becomes a PMA in terms of the data collected. The only way to collect somewhat robust data is to keep

these devices in Class III, at least until the MDR failures begin to fall. It is imperative for the FDA and industry to monitor the use and results of these devices.

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