

**515(I) REGULATORY CLASSIFICATION OF AUTOMATED EXTERNAL
DEFIBRILLATORS**

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FDA Executive Summary

Circulatory System Devices Panel
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Automated External Defibrillators
515(i) Reclassification

1. INTRODUCTION

Automatic external defibrillators are low energy devices with rhythm recognition detection systems that deliver an electrical shock of energy used for defibrillating the atria or ventricles of the heart. Although classified into class III, the most high risk device type, AEDs have not been subject to the requirement of submitting a premarket approval (PMA) application to demonstrate affirmatively a reasonable assurance of safety and effectiveness. Instead, they have been allowed to enter the market following FDA clearance of a 510(k) submission, usually reserved to lower risk devices.

In January 2009, the Government Accounting Office (GAO) recommended that the FDA take steps to issue regulations for class III device types currently allowed to enter the market via the 510(k) process (including AEDs) by either requiring PMAs or reclassifying them into Class I or Class II [GAO-09-190]. On April 9, 2009, FDA issued a Federal Register Notice [Docket No. FDA-2009-M-0101] requesting safety and effectiveness information from manufacturers to determine whether AEDs should remain in Class III, requiring PMAs, or whether they should be reclassified into Class I or II.

To assess the safety and effectiveness of AEDs, FDA has conducted an independent, comprehensive, systematic review of the scientific literature and other information, including a summary of the performance testing currently required for premarket applications, an analysis of recalls submitted over the past 5 years, and an analysis of medical device reports (MDRs) as they relate to issues of engineering design, quality management and studies of electrophysiological issues. The purpose of this advisory panel meeting is to supplement FDA's review with expert recommendations regarding the safety and effectiveness of AED devices to determine whether sufficient information exists to develop special controls to adequately mitigate the risks of AEDs to the point that they could be reclassified into Class II.

2. BACKGROUND ON THE RECLASSIFICATION PROCESS

Upon enactment of the Medical Devices Amendments of 1976, the FDA was required to classify all existing device types – known as preamendments devices – into one of three risk-based classes: Class I, II, or III. Class I devices are generally exempt from premarket review, whereas Class II devices generally require FDA clearance of a premarket notification (510(k)) submission showing substantial equivalence to a device for which reasonable assurance of safety and effectiveness has already been established. Class III devices generally require approval of a premarket approval application (PMA) demonstrating a reasonable assurance of safety and effectiveness before they can be marketed in the United States.

Generally, devices that were on the market before May 28, 1976, the date of enactment of the 1976 amendments, and devices marketed on or after that date that are substantially equivalent to

such devices, have been classified by FDA. “Preamendments devices” are those class III devices that were on the market before May 28, 1976, and the devices found to be substantially equivalent to them that were marketed on or after that date. Although section 515(b)(1) of the act (21 U.S.C. 360e(b)(1)) establishes the requirement that a preamendments device that FDA has classified into class III is subject to premarket approval, such devices were not *automatically* subject to the requirement of submission of a PMA. Rather, under section 515(b) of the Federal Food, Drug, and Cosmetic Act (the act), the FDA is required to either “call for PMAs,” a process requiring notice-and-comment rulemaking, before requiring premarket approval for a class III preamendments device, or FDA must formally reclassify such devices into class I or class II, such that FDA may appropriately regulate those devices through the 510(k) process.

Despite this statutory requirement, the FDA has allowed class III preamendments devices that have not been the subject of a call for PMAs and have not been reclassified to enter the market by submission and clearance of a 510(k) application. The result is that, although FDA intended to use the 510(k) process as a temporary measure for class III preamendment devices, some preamendment devices, including AEDs, remain in class III but are still subject only to clearance of a 510(k).

Section 515(i) of the act directs FDA to either revise the classification of the device into class I or class II, or require the device to remain in class III. The FDA is holding this panel meeting to determine whether AEDs should remain in class III and be made subject to PMA or be reclassified. For devices remaining in class III, section 515(i) requires FDA to establish a schedule for the promulgation of a rule requiring the submission of PMAs for the device.

Below is a further discussion of each of the classes as well as the key factors that should contribute to the discussion and to the assessment of recommended class for the device type.

Class I

Class I devices are low risk devices for which general controls are adequate to assure a reasonable assurance of safety and effectiveness. General controls include registration and listing with the FDA, compliance with the Quality System regulation, reporting of adverse events and other regulatory controls that apply to all devices except for those that have been explicitly exempted. It has been historically uncommon for devices to be reclassified from Class III to Class I.

Class II

Class II devices are moderate risk devices for which special controls in addition to general controls are necessary to provide a reasonable assurance of safety and effectiveness. Special controls include:

- Performance standards
- Postmarket surveillance
- Patient registries
- Guidelines (including clinical data)

Special controls may be in the form of specific labeling requirements, specific testing (bench, animal, and/or clinical) requirements, device design requirements, or other requirements.

The key factor in being able to develop special controls is the ability to sufficiently characterize the risks presented by devices categorized in the device type and to develop means of controlling the risks. For example, in the case of a device that has a mechanical component, in order to develop a special control for this feature, one should be able to identify the required bench test,

including test protocol and acceptance criteria, that assesses the mechanical integrity of the device.

A device type reclassified into Class II would likely require submission of a 510(k) prior to marketing and would need to comply with all of the special controls designated for the device type.

Class III

Class III devices are the most high risk devices. These devices require approval by FDA of a premarket approval application demonstrating a reasonable assurance of safety and effectiveness for the device. Were the FDA to determine that AEDs should remain in class III, the FDA would call for PMA applications and devices already on the market through the premarket notification (510(k)) program would be required to submit PMA applications and attempt to seek market approval under a new PMA. In addition, all future devices would need to seek market entry through submission of a PMA application. Devices regulated under PMA have additional requirements (both premarket and postmarket) beyond what is required for 510(k) applications and, accordingly, the PMA program is considered to be the most rigorous type of marketing application.

One primary reason for sustaining the Class III categorization is if the device type is of high risk, and thus, warrants the additional controls and rigor necessary to properly determine the safety and effectiveness of the device.

Another reason to sustain the Class III categorization is if one is unable to develop special controls to sufficiently characterize the requirements needed for the device type. For example, if the types of devices vary significantly from each other, it may be difficult to develop the types of requirements that may be generalized to all devices seeking market entry in the future.

As you proceed through the materials presented in this executive summary as well as the information presented at the Advisory Panel Meeting, you will be asked for your recommendation of the appropriate classification (either Class I, II, or III) for the device type. In doing so, you will be considering the level of risk associated with the device type as well as the ability to develop and identify special controls that would be applied to the device type. In the case where you recommend that the device type be reclassified into Class II, FDA will request that you discuss the special controls that would be required.

3. PANEL MEETING PURPOSE

The purpose of this panel meeting is to discuss and make recommendations regarding regulatory classification of Automated External Defibrillators to either reconfirm to class III (subject to premarket approval application [PMA]) or reclassify to class II (subject to premarket notification [510(k)s]), as directed by section 515(i) of the Federal Food, Drug and Cosmetic Act.

4. DEVICE DESCRIPTION

An automated external defibrillator (AED) is a device with a rhythm recognition detection system that delivers into a 50 ohm test load an electrical shock of a maximum of 360 joules of energy to

treat ventricular fibrillation or pulseless ventricular tachycardia. An AED analyzes the heart rhythm, identifies whether the rhythm is shockable or non-shockable, and automatically delivers an electrical shock (fully automated AED), or advises the user to deliver the shock (semiautomated or shock advisory AED). The main components of the defibrillator can be separated into hardware and software components. The hardware components include an electronic circuitry that detects and records the cardiac rhythm, a battery (accessory) that supplies the electrical current for the defibrillation shock and a capacitor that stores and discharge the proper dose of the defibrillation shock. The software analyzes the cardiac rhythm, decides whether the rhythm is shockable or non-shockable and based on this decision either discharges the energy stored in the capacitor into the defibrillation electrodes (shockable rhythm) or discharges the energy into an internal resistor (non-shockable rhythm). The software also commands the voice prompts that guide the user and monitors and self diagnose the proper functioning of the device.

The defibrillation system consists of other accessories besides the defibrillator itself. These accessories include: batteries, defibrillation electrodes (adult and pediatric), cables and adapters.

AEDs can be fully automatic or semiautomatic. 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. Fully automatic defibrillators deliver a defibrillation shock if commanded by the device software without user intervention. These types of devices are used by trained users in homes, public access defibrillation (PAD) programs, Emergency Medical Systems and hospitals. In addition to the exclusively automated devices, there are more complex devices that include monitoring capabilities (ECG, SpO₂, NIBP, EtCO₂, etc), manual defibrillation and automated defibrillation. These monitor/defibrillators are used by professionals mostly in Emergency Medical Systems and hospitals.

Currently all AEDs are sold by prescription, except for one that is available for over-the-counter (OTC) use. The sponsor of the OTC AED provided data to demonstrate that its device could be safely and effectively used by lay people based on written instructions, voice and visual prompts from the device and the device itself (designed around human factors). The OTC AED was presented before the Circulatory System Devices Panel on July 29, 2004 prior to FDA granting its market entry (clearance). Both prescription and OTC AEDs are tracked devices. In its discussion at the July 2004 panel meeting, the panel agreed that a tracking system should be developed for different contingencies, for example: to communicate changes in resuscitation protocol or in the case of recalls.

5. 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.

6. DISCUSSION OF RISKS TO HEALTH

AEDs are devices that diagnose life-threatening abnormal heart rhythms, or cardiac arrhythmia, and treat them by delivering electrical energy to the heart to restore its normal rhythm. Each year, nearly 300,000 Americans collapse from sudden cardiac arrest, a condition characterized by

non-life-sustaining cardiac rhythms. Most often these cardiac rhythms are ventricular fibrillation or pulseless ventricular tachycardia. The survival of these patients depends upon a rapid sequence of rescue events that follow the successful delivery of a defibrillation shock from the AED. Rescuers have only minutes before these rhythms degenerate beyond rescue capabilities.

AEDs are now found in airports, community centers, schools, government buildings, and other public locations. These devices are intended for use by the general public, but most require a prescription from a physician for purchase. Outside of hospitals, AEDs are used by emergency medical personnel and first responders such as police. AEDs are also found in homes where they are intended to be used by minimally trained or untrained individuals. In the clinical setting, monitor/defibrillators (with AED mode) are used in emergency rooms, intensive care units (ICU) and throughout the hospital by trained professionals.

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. The AED industry has conducted approximately 68 recalls in the past 5 years, affecting hundreds of thousands of devices. Additionally, FDA has received 23,591 medical device reports (at the time of the analysis) for AEDs, including some where the device failure occurred during a rescue attempt and may have contributed to patient harm or death. A detailed discussion of these risks is provided in the Comments section below.

7. MANUFACTURER RECOMMENDATION FOR RECLASSIFICATION

All current manufacturers of AEDs submitted separate reclassification petitions (reclassification of AEDs from class III to class II) in response to the 515(i) order. These manufacturers are:

- Cardiac Science Corporation
- CU Medical Systems, Inc
- Defibtech LLC
- Heartsine Technologies, Inc
- Philips Medical Systems
- Physio-control Corporation
- Zoll Medical Corporation

The primary basis that each manufacturer presented to support the reclassification to Class II was that special controls already exist and could provide reasonable assurance of the safety and effectiveness of AEDs. Examples of applicable special controls that were cited include:

- Testing to industry standards
- AHA Guidelines
- Device labeling
- Guidance documents
- Postmarket surveillance

There are several AED standards for hardware, software, human factors, risk management, wireless communications, etc., with the most commonly used standards as follows:

- ANSI/AAMI DF80: Medical electrical equipment - Part 2-4: Particular requirements for the safety of cardiac defibrillators (including automated external

- IEC 60601-2-4: Medical electrical equipment - Part 2-4: Particular requirements for the safety of cardiac defibrillators and cardiac defibrillator-monitors.

8. FDA ANALYSIS

FDA has conducted an independent, comprehensive, systematic review of the scientific literature and information regarding the safety and effectiveness of AEDs. In particular, the section below describes:

- a summary of the performance testing currently required for premarket applications;
- an analysis of recalls submitted over the past 5 years; and
- an analysis of medical device reports (MDRs) as they relate to issues of engineering design, quality management and studies of electrophysiological issues.

Summary of Performance Testing

In instances where performance testing is conducted, FDA performs an analysis of the differences between the new (or modified) device and the “predicate” device. The predicate device is defined as a device that is currently legally marketed and which was cleared to market through the 510(k) program. For purposes of this section, the term “modified” refers to any type of modification that may impact the safety and effectiveness of the device. Typical modifications to AEDs include changes in waveform, new features, user interface, software and energy delivery. The following is a summary of testing that FDA typically requests for new or modified AEDs:

- a) **Bench testing.** FDA requests engineering testing of new features or components in hardware and software as well as the compatibility of the changes, i.e., electromagnetic compatibility, wireless coexistence, etc. This type of testing includes the defibrillation waveform in the form of oscilloscope captures and waveform parameters measurements in order to compare the equivalence between the waveforms of the new and existing devices.
- b) **Animal testing.** FDA typically requests animal testing when a new defibrillation waveform is not identical to the predicate, but the difference is not significant enough that it requires clinical testing. Animal testing is also used in the confirmation of safety and effectiveness of an AED in pediatric defibrillation. Animal studies are also used to test new features that can improve defibrillation and resuscitation, such as new sensors, algorithms, assistance for CPR, etc.
- c) **Clinical testing, premarket.** FDA requests clinical studies for new defibrillation waveforms that are significantly different from existing waveforms. The endpoints of these clinical studies include defibrillation success, restoration of spontaneous circulation, hospital admission, and hospital discharge. Clinical studies are also requested to evaluate new features that are intended to improve defibrillation and resuscitation, or features that seek to add pediatric indications to devices previously cleared to market for adults. The endpoints for these studies are based on the changes or new features proposed.
Human factor studies are conducted for new AEDs, new features that require user intervention such as device screens, control dials, voice prompts, etc., and devices intended for over-the-counter (OTC) use.

- d) **Clinical testing, postmarket.** Postmarket clinical studies have rarely been used as a tool in the safety and effectiveness evaluation of AEDs. Over the past 7 years, one such study was required for a device intended for OTC use and which collected information on at least 200 uses or for 3 years. Postmarket studies have also been conducted to support pediatric (less than 8 years old) uses.

In its evaluation of the testing for AEDs, FDA believes that engineering data would be better reviewed under PMAs due to the criticality of the AED functions. Significant changes in technology make it difficult to apply the concept of substantial equivalence, i.e., device characteristics cleared 10 years ago, may not be adequate now

With respect to a firm's quality assurance activities, mechanical or electrical failures tend to be the dominant concern with AEDs. According to a recent FDA recall analysis, "nonconforming material/component" types of failures have provided 49.2% of the root causes for the AED malfunctions. Examples of "nonconforming material/component" failures include electrical resistors out of specification, high voltage capacitors out of specification, and a printed circuit board supplier failing to properly remove solder flux from PC boards used in AEDs. Device design failures include construction with improperly specified insulation and improperly designed battery compartments, selection of an unstable voltage reference, and failure to operate at low temperatures.

In quality management, there is a large group of device malfunctions that result from inappropriate components being supplied by vendors to the device manufacturer. These malfunctions are the direct result of improper engineering processes and controls. These generally fall into two categories:

- replacement components that do not meet the complete component specifications; and
- unreported changes in the vendor's fabrication process which might inadvertently affect the component performance.

Based on the level of review and the depth of testing, FDA believes that human factors studies for AEDs used by minimally trained or lay use are most appropriately reviewed under PMA.

However, human factor studies of professional-use devices could be appropriately reviewed under either 510(k) or PMA because the level of testing is designed for users with significantly more training than lay users.

Animal data is submitted as supporting data to clinical studies or as stand alone data to demonstrate the safety and effectiveness of a modified shock waveform, a new feature or a new device. Although bench and animal testing are tools used to evaluate the equivalence of one device to another, in some cases the concept of substantial equivalence becomes challenging because there is nothing to compare to. Therefore, it seems more adequate to review these studies under PMAs.

FDA has historically required clinical data for new defibrillation waveforms. The preferred study design has been a prospective randomized clinical study in order to obtain unbiased high quality data to permit an evaluation of the safety and effectiveness of the new waveform. The need and design of the clinical study would be the same, regardless of regulatory pathway, because the study design is driven by the new shock waveform that is requested

FDA believes that the developing field of AEDs involved with optimizing defibrillation shocks during CPR warrants clinical evidence to establish clinical performance and to optimize the sensitivity and specificity of the arrhythmia detection algorithms that are used. FDA notes that the optimization of therapy delivery is an unmet challenge and supports the development of these new technologies. FDA appreciates the sensitivity that a higher regulatory threshold may inhibit device development and innovation and considers this tradeoff with the need to evaluate the appropriate level of testing for AEDs.

MDR Analysis

FDA performed an analysis of medical device reports (MDRs) from the Manufacturers and Users Device Experience (MAUDE) database for AEDs. Specifically, the analysis was done with the AED-specific device product code “MKJ” and for the time period January 1, to March 31, 2010. During this reporting period, there were 23,591 MDRs, which were classified into the following categories:

Table 1: Event Type by Year

| Year | Death | Injury | Malfunction | Other | Invalid | Totals |
|-------------|--------------|---------------|--------------------|--------------|----------------|---------------|
| 2005 | 126 | 11 | 3084 | 93 | 22 | 3336 |
| 2006 | 103 | 20 | 3130 | 153 | 17 | 3423 |
| 2007 | 118 | 9 | 3694 | 18 | 12 | 3851 |
| 2008 | 108 | 18 | 4594 | 4 | 14 | 4738 |
| 2009 | 184 | 15 | 6484 | 58 | 1 | 6742 |
| 2010 | 82 | 5 | 1396 | 12 | 5 | 1501 |
| Totals | 721 | 78 | 22382 | 338 | 71 | 23591 |

Unlike the MDR reporting for many other medical devices, the MDRs above do not necessarily represent events experienced during device use, because the failure in some cases may have been reported when no patient was involved, e.g., by the self diagnostics of the device. Death reports by definition are associated with a device malfunction but are sometimes submitted before the final analysis by the manufacturer is complete. It is possible then that the final determination is that the device did not cause or contribute to the death.

The numbers of reports without follow-up by the manufacturer were also analyzed. It is common for manufacturers to submit an initial report with only the device problem but state that they will submit a follow-up report when their investigation is complete. This analysis concluded that only 7,916 (33.5%) reports were evaluated by the manufacturer from the 23,591 reports. Two possibilities may have likely contributed to the poor follow-up. First, user facilities can be reluctant to send the device to the manufacturer. Unless the manufacturer ships a replacement device while the original is being evaluated, the user facility has one less defibrillator to use. Second, many manufacturers submit an MDR as soon as possible to meet the 30-day reporting requirement set by FDA. The MDR will contain the device information, event description, and problem code but the device has not been evaluated.

Overall, FDA has the following remarks regarding the MDR analysis:

- Total reporting has substantially increased over the evaluated time period. It has more than doubled in the last 5 years. The increase has been evenly distributed among event types and among the top device problem codes.

- Approximately 66% of failed devices never 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 a trend analysis or comparative data for the most common failure modes.
- Annual reporting would improve overall surveillance by providing denominator data for device distribution as well as current trend information on issues being followed by the manufacturer.

Based on these conclusions, from an MDR analysis perspective, FDA believes that regulation of AEDS as Class III device with PMAs would be the most appropriate regulatory pathway.

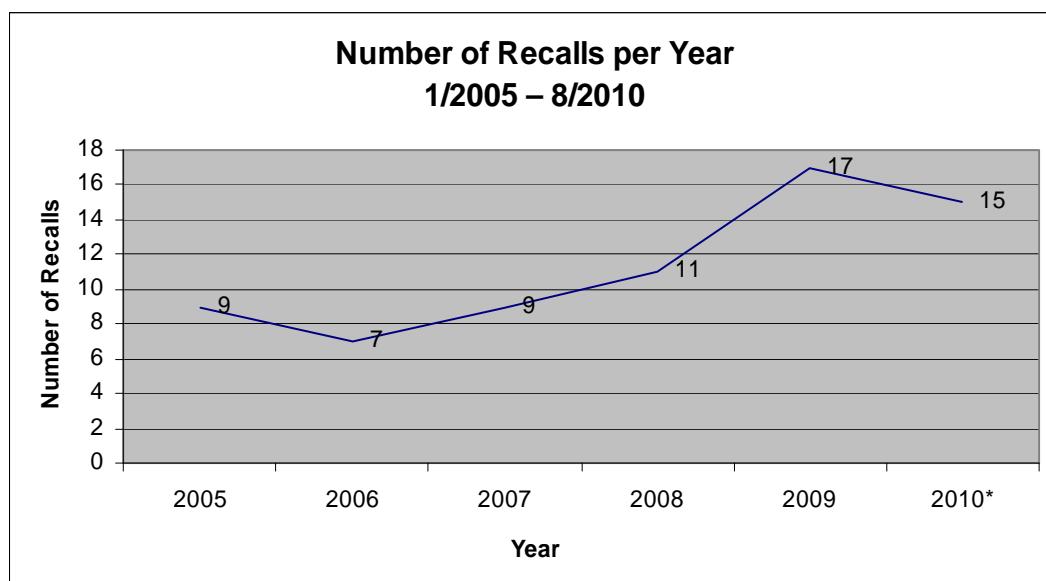
Recall Analysis

From January 2005 – August 2010, a total of 68 recalls were conducted by medical device manufacturers for devices classified under the product code MKJ, which includes AEDs and monitor/defibrillators with AED mode. Of the 68 recalls, 17 were classified as Class I, 48 were classified as Class II, 1 was classified as Class III, and 2 were considered to be safety alerts. The following are the definitions of the type of recalls:

- **Class I recall:** a situation in which there is a reasonable probability that the use of or exposure to a violative product will cause serious adverse health consequences or death.
- **Class II recall:** a situation in which use of or exposure to a violative product may cause temporary or medically reversible adverse health consequences or where the probability of serious adverse health consequences is remote.
- **Class III recall:** a situation in which use of or exposure to a violative product is not likely to cause adverse health consequences.

Figure 1 shows the number of recalls per year for the same period. Since 2009, FDA has observed a dramatic increase in the number of reported recalls.

Figure 1: Number of Recalls Classified by Year



FDA analyzed each of the 68 recalls of AEDs to determine the most appropriate reason why the recall occurred. With the exception of one recall related to the distribution of a device without a 510(k), the remaining recalls could be reasonably related to product defects resulting from certain failures of a manufacturer's quality system. Each of the remaining 67 recalls were further evaluated to determine the most appropriate Quality System (QS) regulation failure associated with each recall. Table 3 describes how failures of different requirements of the QS regulation can lead to the release of defective product and necessitate a recall.

Table 3: Description of Quality System Deficiencies

| Quality System Regulation Deficiency | Description |
|---|---|
| Purchasing Controls and Receiving Acceptance Activities | A recall identified under this category can be attributed to several factors including problems at the device manufacturer or their vendor/supplier. The vendor/supplier could have provided a component that did not meet the manufacturers specifications. For example, the vendor may have made a change to the design or manufacturing of the component that the manufacturer was unaware of. In addition, the manufacturer may not have identified the component that was out of specification during the receiving acceptance activities performed during receipt of the component from the vendor/supplier. 21 CFR 820.80(b), 820.50 |
| Design Controls | A recall identified under this category can be attributed to several factors including changes to the design or software of the device or problems with the original design of the device. For example, the finished device did not perform reliably as intended during use, although it met the approved original specifications and was not adversely affected by the manufacturing process or use of a defective component or material, and was properly used according to labeling. In addition, components/materials selected/designed for an application did not perform reliably as intended although they met the original or modified specification and were not adversely affected by the manufacturing process. A manufacturer could have also made changes to the design of the device (including software) that were not properly tested (validated) prior to implementation and subsequently caused an adverse effect on the finished device. 21 CFR 820.30 |
| Production and Process Controls and Process Validation | A recall identified under this category can be attributed to the manufacturing of the device. The execution of the production or manufacturing process was not adequately controlled or validated resulting in an inadequate process or adverse effect on the product being processed. 21 CFR 820.70, 820.75 |
| In-process and Final Acceptance Activities | A recall identified under this category can be attributed to in-process and final acceptance activities performed by a manufacturer on components, sub-assemblies, or finished devices during manufacturing of the devices. 21 CFR 820.80(c) or (d) |

Figure 2: Approximate Percent of AED Recalls Attributed to Certain QS failures (n = 67)

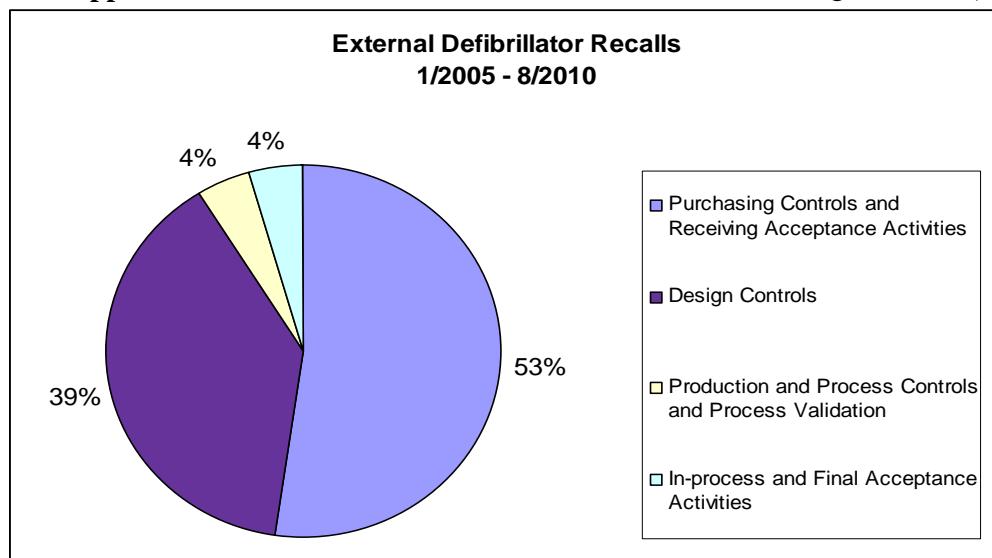


Figure 2 displays the percent of recalls that resulted predominantly from a failure of particular QS regulation requirements. The majority of recalls that have occurred since 2005 can be mainly attributed to issues associated with the firm's handling of purchasing controls or design controls.

Manufacturers of AEDs are frequently inspected by FDA. These inspections often result in FDA taking additional actions to warn the manufacturers about their violative practices. For example, in 2006, AEDs were included in a Risk Based Work Program (RBWP) in which FDA conducted nine inspections of AED manufacturers. Four of these nine inspections resulted in a classification of Official Action Indicated (OAI) and the issuance of at least two Warning Letters. An OAI classification requires a manufacturer to take certain corrective actions.

Since 2005, a total of nine Warning Letters have been issued to manufacturers of AEDs citing the manufacturers for violations of the Quality System (QS) [21 CFR 820], Medical Device Reporting (MDR) [21 CFR 803], Corrections and Removal [21 CFR 806], and Device Tracking [21 CFR 821] regulations. Eight out of nine Warning Letters contained some type of QS deviations noting issues with the firm's manufacture and control of the devices.

In order to help provide additional assurances and potentially prevent some of the issues identified in postmarket inspections or through recalls of the devices as described above, FDA believes that the following types of controls and requirements that are a part of a premarket approval (PMA) application should be placed on AED manufacturers, including:

- Premarket review of manufacturing information including a manufacturer's procedures and processes to ensure that they comply with the requirements of 21 CFR 820.
- Pre-approval inspections to determine manufacturer's compliance with the QS regulation which allows for assurances that the manufacturer's systems are in place and appear to be adequate prior to the manufacture and distribution of the devices.
- Review of any changes in manufacturing facilities to ensure that the manufacturer's facility, procedures, and systems are adequate prior to the manufacture and distribution of the devices. This requirement is called a site change supplement.

- Additional postmarket assurances through the PMA program including the postmarket review of significant manufacturing changes to ensure that the changes are adequately evaluated and tested prior to implementation and the annual reporting of manufacturing changes to gain a better understanding of the types of changes that are occurring and the reasons for those changes. This requirement is called a 30-day notice.

Based on the postmarket information collected on AEDs including recall and inspection data and FDA's current methods of handling AEDs after they are cleared, FDA suggests that some of these issues may have been mitigated and more appropriately handled through the more stringent review process and controls required by a PMA application. In summary, from a device recall perspective, FDA recommends that the AEDs be reclassified as Class III devices that require a PMA application.

Additional FDA Perspective Regarding Overall Classification

While the rest of this summary reflects the primary FDA perspective regarding issues for consideration in a classification discussion, the section below presents a minority FDA perspective. We request that this perspective also be considered in your deliberations and analysis.

The field of AEDs has seen significant advances to the technology and capabilities over the years. These advances have been with modifications to existing devices that were previously granted market entry by FDA as well as with the introduction of new AED devices. The overall goal for these modifications and advances has been to provide "better" resuscitation intervention to patients, at the core of which are both defibrillation/cardioversion and cardiopulmonary resuscitation.

Historically, FDA has regulated AEDs under the 510(k) program. If FDA chooses to reconfirm the status of AEDS as Class III medical devices, and calls for PMA applications, FDA would then apply the rigorous constraints of the PMA regulation to any and all new iterations of AEDs. 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 US, 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. Potentially, FDA could couple this reclassification to Class II with a strengthening of the 510(k) process with the establishment of appropriately-chosen special controls. Finally, the classification of AEDS into Class II 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, etc.

It is acknowledged that there are potential downsides to regulation of AEDs as Class II devices, instead of Class III. An example is the limited ability to have oversight of changes to legally marketed devices. However, it may be possible to appropriately regulate these devices to address these issues.

The above commentary is presented so that the Panel may consider the various key perspectives for consideration on this issue.

9. DISCUSSION OF RECOMMENDATION

Each year, nearly 300,000 Americans collapse from sudden cardiac arrest, a condition characterized by non-life-sustaining cardiac rhythms. Most often these cardiac rhythms are ventricular fibrillation or pulseless ventricular tachycardia. These patients' survival depends upon a rapid sequence of rescue events that includes the successful delivery of a defibrillation shock from the AED. Rescuers have only minutes before these rhythms degenerate beyond rescue capabilities. AEDs are now found in airports, community centers, schools, government buildings, and other public locations. A recent publication reported that application of an AED by bystanders seems to save 474 lives per year and is associated with nearly a doubling of survival after out-of-hospital cardiac arrest.(1) These results are comparable with the 2-fold AED survival benefit demonstrated in the randomized and controlled PAD trial.(2,3) FDA fully appreciates the need to increase the availability of safe and effective AEDs in the public setting.

In light of the important role that AEDs have within the public health and the importance of their availability, FDA has conducted its exhaustive analysis of a wealth of information that includes data reviewed in premarket applications, analysis of adverse event reports, AED recalls, and information from FDA inspections of manufacturers, and peer-reviewed literature.

FDA has been charged with making a recommendation with regard to the regulatory classification of Automated External Defibrillators to either reconfirm to class III (subject to premarket approval application [PMA]) or reclassify to class II (subject to premarket notification [510(k)s]), as directed by section 515(i) of the Federal Food, Drug and Cosmetic Act. For this purpose, the FDA review team has carefully analyzed a broad spectrum of requirements to ensure the readiness and reliability of AEDs. This critical analysis resulted in compelling arguments that future marketing submissions should include the following additional requirements:

- 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

If FDA were to reclassify AEDs into class II subject to 510(k), FDA would need to create special controls for each of these scientific and regulatory requirements in addition to the special controls for engineering, software, human factors, animal studies and for clinical studies as proposed by the AED manufacturers. The following table presents a summary of the regulatory requirements for three review paradigms: the current practice standard under 510(k); what a proposed reclassification to class II, 510(k) with special controls would look like; and what a reconfirmation to class III, PMA would look like:

Table 4: Pre-Market and Post-Market Requirements for 510(k)s and PMAs

| Pre-Market Notification 510(k) for Class III AEDs | Pre-Market Notification 510(k) with Special Controls | Pre-Market Application PMA |
|---|---|---|
| Pre-Market Requirements | Pre-Market Requirements | Pre-Market Requirements |
| Bench Testing | Same with special controls | Same |
| Animal Studies | Same with special controls | Same |
| Clinical study design is dictated by questions of safety and effectiveness. 510(k) integrity inspection only if FDA finds a "due cause". Information kept on file by sponsor-open for inspection if product issue | Clinical study design is dictated by questions of safety and effectiveness. A unique special control would have to be created to allow Bioresearch Monitoring (BIMO) inspections for integrity and assessment of sponsor quality/GCP oversight. This would be a first-time special control | Clinical study design is dictated by questions of safety and effectiveness. PMA pivotal sites undergo BIMO inspections for integrity and assessment of sponsor quality/GCP over site |
| | Premarket review of manufacturing information. Unprecedented special control | Premarket review of manufacturing information |
| | Pre-approval inspection. Unprecedented special control | Pre-approval inspection |
| | | |
| Post-Market Requirements | Post-Market Requirements | Post-Market Requirements |
| | Review of any changes in manufacturing facilities. Unprecedented special control. | Review of any changes in manufacturing facilities |
| | Postmarket review of significant manufacturing changes. Unprecedented special control. | Postmarket review of significant manufacturing changes |
| 522 Postmarket Surveillance Studies | 522 Postmarket Surveillance Studies | Post-Approval studies |
| | Annual reporting. Unprecedented special control. | Annual reporting |

This table clearly shows that the additional requirements recommended for improved pre- and post-market review of AEDs are already integrated in the PMA paradigm. FDA would have to create special controls under 510(k) to request requirements that are already called for under PMA. Moreover these special controls would be without precedent in many circumstances and would consequently be quite challenging to develop. Therefore, it does not seem appropriate to create an equivalent parallel regulatory paradigm that would significantly blur the line between a 510(k) and a PMA when the PMA paradigm already provides for the increased regulatory oversight that is recommended for AEDs.

AED Accessories

The main accessories for AEDs are:

- Defibrillation electrodes
 - Pad electrodes - semiautomatic and automatic defibrillation
 - Paddle electrodes - manual defibrillation
 - Spoon electrodes – Internal defibrillation
- Batteries
 - Rechargeable
 - Non – rechargeable
- Adapters and cables

These accessories are critical components of the defibrillation system and require similar requirements and controls as the defibrillator to ensure the safe and effective delivery of therapy.

Summary Recommendation

It is the overall recommendation by FDA that AEDs be classified as Class III medical devices and be subject to the regulations in accordance with premarket approval (PMA) applications.

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