

Philips Medical Systems

Docket 199N-0418 Additional Information

Via Federal Express

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Dockets Management Branch
Food and Drug Administration
Room 1061
5630 Fishers Lane
Rockville, MD 20852

Reference: Docket No. 199N-0418
Reclassification of Automated External Defibrillators
Federal Register Vol. 68, No. 208
Dated: October 28, 2003

To whom this may concern:

The following is provided in response to FDA's correspondence dated July 13, 2005 requesting additional information regarding Philips' comments on the above referenced docket. The questions asked by the Agency are denoted in **bold text** and Philips' response is denoted by regular text.

- 1. You suggest that the results from ease of use testing will be sufficient to ensure that a defined level of human factors standards has been met. To include this in a special controls guidance document, FDA will need to more fully define the scope of such usability testing. Please comment on what aspects of usability are considered most critical. Please offer a proposal for how to appropriately conduct these studies in terms of methodology, sample size, and pass/fail criteria.**

Successful emergency responses with automated external defibrillators (AEDs) depend on both users and their devices. User-specific product design can positively influence user success in time-critical emergency situations. Therefore, user testing is crucial in evaluating AED design. We believe such user studies should have two endpoints: efficacy and safety. We believe usability testing is important for both over-the-counter (OTC) and prescription devices. However, we also believe there are some additional requirements for OTC status because



anyone might purchase the device. Details of usability studies, including methodology, sample size and pass/fail criteria, are included in this communication as Attachment 1.

Furthermore, we believe that potential representative users should formally evaluate the labeling used during an emergency situation during the product development cycle and be part of the submission review process. Again, we believe there are differences in the usability studies to assess the labeling when the defibrillator carries the prescription caution labeling and when it does not. Recommendations related to the study design, methodology, acceptance criteria, reporting, etc. for assessing the labeling used during an emergency use are included in this response as Attachment 1.

- 2. In order to create a special controls guidance document, it is necessary to identify all the risks associated with a device and the ways in which special controls can be used to mitigate those risks. Please provide your assessment of the risks associated with the use of AEDs, and the special controls that can be used to mitigate them. Please comment on whether over-the-counter status of these devices raises new risks, and if so how they would be mitigated by special controls.**

Philips supports the FDA Special Controls Guidance Document for Arrhythmia Detectors and Alarmsⁱ and believes there are additional elements regarding the therapy that AEDs provide that should also be considered. Furthermore, as stated in our original comments, the existing automated external defibrillator performance standards and recommendations (i.e., EN 60601-2-4:2002, AAMI DF 80:2004 and AHA algorithm recommendation publicationⁱⁱ) should be formally Recognized Consensus Standards by the FDA. The additional controls should address:

- **Waveform** - Any new AED waveform that utilizes electrical signals significantly outside the scope of safety and effectiveness performance established in the literature should be supported by a prospective, randomized clinical trial using that new waveform. A detailed description of the waveform should be included in the submission and alternatives to the clinical trial should be supported by a scientific rationale also included in the submission.
- **Device Readiness/Maintenance** – Although AEDs may remain in standby for years between actual uses, they are expected to perform reliably when called upon. As such, we believe it is important for manufacturers to disclose during the submission process component design decisions and reliability information. In addition, we believe disclosing this information in a consistent manner in the labeling will allow meaningful comparisons between manufacturers.

- **Additional Features** - AEDs are not designed or used just for defibrillation any more. Manufacturers are incorporating features, such as CPR coaching and fully automated shock delivery. We believe there are additional considerations needed when the features of an AED extend beyond resuscitation.
- **Post Market Study** – We propose that each manufacturer when introducing an AED that impacts patient care for the first time performs a post market study and provides the protocol to FDA during the submission review process.

Details on each of these topics are provided in Attachment 2.

Any risks and mitigations associated with these items should be included in the risk analysis that is reviewed during the submission process.

3. **Facility inspection is one general control that FDA has over quality manufacturing. A Class II 510(k) device does not require premarket review of Quality System information, does not require pre-approval inspections and may potentially be inspected with less frequency than a Class III PMA device. Recent recall history in this product area suggests problems in manufacturing and post-clearance design changes. Please comment on the difference between the two classes and justify why pre-approval review and inspections would not be necessary to control risks.**

Philips notes that recent product issues in the AED product area were related to individual component and design controls failures. Consideration of safety-critical performance is part of the hazard analysis process in which the determination of criticality and risk are part of design controls and already part of the submission review process, regardless of device classification. According to FDA’s May 2005 “Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices,” the device’s Hazard Analysis should be submitted for review for all levels of device concern and therefore, all device classes.ⁱⁱⁱ

We also propose there are other regulatory requirements that address manufacturing and post-clearance design changes since they are required to be followed regardless of device classification:

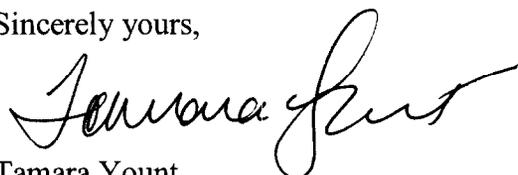
- **Corrective and preventative actions** require verification and validation of the corrective and preventative action to ensure that the action is effective and does not adversely affect the finished device (21 CFR 820.100(a)(4));

- **Production and process changes** require changes to a specification, method, process or procedure to be verified and, where appropriate, validated before implementation (21 CFR 820.70(b)); and
- **Design controls** require that changes be validated, where appropriate verified, reviewed and approved before being implemented (21 CFR 820.30(i)).

We believe, therefore, any additional controls related to device performance should occur during the submission review process based on risk analysis reviews. Using this approach, questions about the device's safety-critical performance are answered pre-market rather than post-market.

Please feel free to contact me if there are any additional questions related to this additional information. Thank you for your consideration in this matter.

Sincerely yours,

A handwritten signature in black ink, appearing to read "Tamara Yount". The signature is fluid and cursive, with a large initial "T" and a long, sweeping underline.

Tamara Yount
Regulatory Affairs

Attachment 1

Usability Studies

Successful emergency responses with automated external defibrillators (AEDs) depend on both users and their devices. Good device design can positively influence user success in time-critical emergency situations. Therefore, user testing is crucial in evaluating AED design. We believe that simulated use (manikin) user testing study design should consist at a minimum of two endpoints: efficacy and safety. We also believe that the labeling intended for use during an emergency (if applicable) should also be assessed. Each of these concepts is expanded below. In addition, the studies should be conducted in accordance with principles of Good Clinical Practices, and data management, such as “Guidance for Industry Computerized Systems Used in Clinical Trials.”^{iv}

1. Device

Efficacy

Design controls require design validation testing to ensure that the device conforms to users’ needs and intended uses.^v We believe that there are different considerations necessary for over-the-counter (OTC) and prescription (Rx) AEDs in supporting this requirement and the testing performed should be based on the lowest-skilled purchaser of the device:

- OTC – Although defibrillator manufacturers encourage training for all AED users, it is not realistic to assume that every OTC AED purchaser will either complete or periodically update training. Accordingly, testing should be designed to measure the ability of users to use the device adequately and safely based upon the labeling provided in the OTC packaging alone. We believe that the requirements for OTC and public access defibrillators for the purposes of demonstrating efficacy are the same. Such testing should serve to assure that the labeling is complete, clear, and does not compromise user performance. Further, some purchasers may not take advantage of all included labeling while becoming familiar with their AED.

Therefore, testing should also include a component that examines adequate use and safety with only the labeling (if any) available to users during emergency use. The user population should consist of users with no medical background or training and no training on any AED. The study sample size should be such that, with a 95% lower confidence level, it is demonstrated that a majority of the users place the pads in a position to likely result in a successful defibrillation shock (as determined by a physician) and deliver the shock.

- Rx – With the labeled intended user group, a minimum of 10 users is recommended based on FDA’s “Do it by Design” guidance.^{vi} It is assumed that these users of a prescription product will receive training and be under the guidance of a physician/medical director/organized response program/medical system so that a lower number of test subjects compared to OTC is acceptable. Testing should occur with the AED and its labeling in the configuration recommended for use during an emergency.

Safety

Safety to the user and patient are paramount regardless of prescription labeling status. We believe, therefore, that it should be demonstrated with a one-sided 95% lower confidence level that users of the AED should not introduce any unsafe, conditions to themselves or the SCA victim that could result in a life-threatening condition or serious injury. An example of unsafe behavior includes touching during shock delivery in such a manner that a shock across the user’s chest could occur. A physician should disposition any unpredicted or unsafe behavior contrary to the labeling by direct observation during the study or by review of videotape or pictures. All touching incidences should be included in the final report and reviewed during the submission process.

The above comments related to safety apply to semi-automatic AEDs (in other words, a button must be pressed to deliver a shock). AEDs that automatically deliver a shock introduce new issues that should be assessed by user studies (e.g., the risk of energy delivery without adequate warning in the presence of one or multiple rescuers treating an SCA victim).

Report Contents

Testing methodology (including pads placement criteria), any materials provided to users (such as scripts, introductions, labeling, background, training, etc., description of test materials (such as the clothes worn by the manikin) and the description device tested (including disclosure of whether it was a production equivalent device or was a training device) should be included in the final report and submitted to FDA during the review process. Justification for sample size, user group and explanations of user exclusions, device anomalies and user demographics should be included in the final report. To reflect ease of use, the elapsed time for each user to perform the assigned tasks, such as from retrieving the AED until shock delivery, should be presented in the final report.

2. Labeling

We believe that the written labeling should be assessed with representative users to ensure it is appropriate. It is also important to ensure that the provided labeling does not interfere with use of the product. Furthermore, there are those that use the device (such as a public access scenario) who may not be responsible for set-up, maintenance, etc. Therefore, we believe there are two types of labeling scenarios that should be assessed and presented during the submission review process:

1. Private, home use – Since treatment of sudden cardiac arrest is time-critical and the benefits of self-test are achieved only with the device being powered, the labeling associated with successful device set-up should be assessed for readability and comprehension. Furthermore, since these products will often be sold directly to consumers who may or may not have experience maintaining an AED, maintenance and proper storage are also important elements for labeling assessment.

This assessment should include a study in which the users can successfully recognize the need for defibrillation (unless the algorithm supports alternate approach), activate emergency medical services (or provide an alternate approach to activating EMS, as appropriate) and complete the resuscitation process. The labeling should be consistent with the recommendations of FDA's "Guidance on Medical Device Patient Labeling; Final Guidance for Industry and FDA Reviewers,"^{vii} FDA's "Write it Right: Recommendations for Developing User Instruction Manuals for Medical Devices in Home Health Care,"^{viii} IEC 60601-2-4 and AAMI DF 80. Furthermore, the labeling should include any relevant hazard information not already disclosed as part of compliance with IEC 60601-2-4 and AAMI DF80. Also, there may be specific requirements of device performance for OTC that may require additional labeling and/or validation depending on the design and requirements of the specific device.

2. Commercial use, public use or professional use – Since these products are sold into environments that typically involve medical directors and program administrators with established defibrillation program policies and procedures, the set-up and maintenance labeling does not require the same level of assessment and readability. Information related to configuration settings and clinical data are appropriate for prescribing physicians and medical directors. The labeling developed should be consistent with relevant labeling guidance, including those mentioned previously for private, home use and the labeling used for emergency use described above.

Attachment 2

Additional Controls

The following summarizes the additional controls that could be used in developing a special controls guidance document. The topics include:

- Waveform
- Readiness/Maintenance
- Additional Features
- Post Market Study

Each of these topics is discussed in detail in this attachment, including Philips proposals for submission requirements.

1. Waveform

We believe that any new AED waveform that utilizes electrical signals significantly outside the scope of safety and effectiveness performance established in the literature should be supported by a prospective, randomized clinical trial using that new waveform. A detailed description of the waveform should be included in the submission with the following elements given additional consideration:

- The use of energy levels outside of the range supported by existing clinical data for similar waveforms;
- Patient voltages (and resulting currents) outside of the range supported by existing clinical data for similar waveforms;
- Waveform phase durations that fall outside of the range supported by existing clinical data for similar waveforms and
- Waveform shapes that differ significantly from cleared waveforms supported by existing clinical data.

For waveforms similar to predicates supported by clinical data but that observe conventional limits on the electrical parameters discussed above, safety and efficacy data based on animal experiments may be acceptable with the following study design considerations:

- Swine are the preferred model (30-40 kg), due to their similarity to humans with regards to cardiovascular system and defibrillation thresholds.
- Since humans exhibit wide variation in transthoracic impedance and swine do not, the entire range of human impedance must be modeled in the experimental study in order to establish safety and efficacy. The preferred method for creating impedance variation in an animal model is to employ external series resistors (to increase impedance) or parallel resistors (to decrease impedance) around the animal so as to create the desired impedance at the AED terminals and generate the correct waveform *shape*. The *dose*, however, must be characterized in terms of the energy delivered *to the animal*. Reporting energy delivered by the AED as opposed to delivered to the animal is inappropriate and may mask toxicity effects since much of the AED dose is harmlessly dissipated in the external resistors.^{ix}
- Because of variations in the shape of the dose-response curve between different defibrillation waveforms, the defibrillation threshold (E_{50}) is not an adequate characterization of AED performance. Clinically acceptable levels of efficacy (e.g., 80-90%) or another acceptable efficacy level must be described at the minimal energy dose provided by the device.
- Studies conducted with fundamentally healthy animals by delivering shocks to short duration VF are insensitive to myocardial dysfunction that might be incurred in an ischemic substrate. Any such study should report, at minimum, all ECG abnormalities that occur following shocks. These include, but are not limited to:
 - Post resuscitation myocardial measures of systolic and diastolic function
 - Conduction block
 - S-T segment shift
 - Increased occurrence of premature contractions (PVC, PAC) or idioventricular beats
 - T-wave inversion
- In the event of a high rate of occurrence of electrical abnormalities in the ECG in response to the defibrillation shock, a study in an ischemic animal model should be conducted. One method for creating global ischemia is by introducing a prolonged period (e.g., 5 or 7 minutes) of untreated VF prior to defibrillation shocks. The study should report animal outcome (resuscitation and survival) as well as hemodynamic performance and left ventricular function (ejection fraction and stroke volume) versus a device with known characteristics. At least 10 animals per study arm or a sample size that appropriately powered non-inferiority analysis should be used when function, outcome or recovery endpoints are being studied. The studies should be conducted in accordance with Good Laboratory Practices.^x

Alternatively, if an in-vitro model is used to generate any of the above data, then the model should be validated, and the supporting data provided in the submission.

2. Readiness/Maintenance

Unlike most medical devices, AEDs may remain in standby for years between actual uses. Nevertheless, AEDs are expected to perform reliably when called upon. Therefore, readiness is an essential AED design feature.

AED users should have a realistic expectation of device readiness during long intervals between AED uses. Accordingly, AEDs should include active alarms/indicators of the device's readiness status. If such indicators are not provided, a study demonstrating the reliability and readiness of the device for its intended product life cycle should be performed and the results included in the submission and data included in the labeling.

A description of the methods employed in the AED design to assure device readiness should be included in the submission review process. These methods include, but are not limited to:

- 1.) Periodic or aperiodic self-testing of the device.
- 2.) User initiated testing of the device.
- 3.) Periodic or aperiodic inspections of the device.
- 4.) Inherent reliability.

Labeling claims of readiness for use should be substantiated. Design and implementation of self-testing functionality may vary significantly between AED manufacturers. The user's expectation is that a device that performs self-test is providing a high degree of assurance that it will be ready to use when called upon. In addition, a labeling guidance should be prepared such that comparison between manufacturers can be made and for FDA's consistent review of submission. FDA should include a minimum data set to be disclosed in product labeling related to readiness and maintenance, including specifying the format for purchasers to make meaningful comparisons. For example, if a manufacturer wishes to claim a 'readiness for use' indication, it would be appropriate to review evidence during the submission process that demonstrates that the device meets (through any combination of the previously mentioned test methods) a probability of functioning per performance specifications > 99% (suggested). Furthermore, the manufacturer should explain why the test methods chosen are appropriate for the use model and intended AED user/maintainer.

The following methods could be employed to derive an estimate for the readiness for use criteria.

1. Inherent reliability data can be obtained from analysis of historical performance of products with similar complexity, stresses and manufacturing methods.
2. Self-Test coverage can be analyzed by traditional Failure Modes and Effects Analysis (FMEA) or Fault Tree Analysis methods. For periodic testing, consideration of the test interval relative to the use interval needs to be taken into account.
3. Ability of the intended user to inspect for critical functions that falls outside of the self-test regime.
4. For devices that claim readiness for use based on 'inherent reliability,' the manufacturer should maintain an active reliability assessment program to assure that devices are meeting their expected field performance.

Continued AED readiness may depend on at least some periodic maintenance by owners. The intended user and/or maintainer for the AED should be identified so that assessment of the appropriate readiness technology is possible. For example, if inspections are critical to the assessment of device functionality, it should be demonstrated that the intended users are capable of correctly performing the inspections.

Design details and information on consumables associated with AEDs, such as battery chemistry, should be considered during the submission review process. Any special handling, hazard conditions, mitigations or disposal considerations associated with user safety should be disclosed in the product labeling and supported by design information and/or validation data.

3. Additional Features

Many AEDs are no longer used or designed solely for defibrillation. Manufacturers are incorporating features and functionality that extend the use of AEDs for resuscitation purposes as well as monitoring/diagnostic purposes. Additional features recently incorporated into AEDs, for example, include CPR coaching and fully automated shock delivery. The manufacturer should strive to not introduce or implement new features in a manner that would cause responder confusion in fulfilling the clinical function of the AED.

New features should be considered during the design development and be validated as part of a system. Testing should show that the new features and/or compatible accessories do not interfere with the defibrillation process or other accessories.

We believe that any claims associated with additional clinically significant features incorporated into the AED should be supported by user studies and/or validation via clinical or animal studies. A final report of these studies should be prepared and submitted to the FDA during the review process. User studies should include efficacy and safety end points using the methodology described above (as applicable).

CPR Coaching

If an AED incorporates CPR coaching, the feature should be supported by appropriate validation. For instance, claims of clinical efficacy of CPR assistance must be supported by clinical trial data. Therefore, if a manufacturer wishes to make clinical claims with regard to CPR coaching, they should perform an appropriate clinical trial to establish a benefit. Conversely, claims of usability and compliance to protocol/guidelines may be based on manikin studies. Unless clinical outcome data is available, CPR assistance claims should be limited to the effectiveness of the coaching system in having the user perform CPR according to current accepted practice.

Refer to Attachment 1 of this document for elements to consider when developing the design validation studies necessary to support feature claims.

Automated Shock Delivery

Although the defibrillator standards address automated shock delivery, the following additional information should be considered when assessing a device designed for automatic shock delivery:

1. Intended users – Does the feature provide a positive benefit to the user group?
2. Environment and likely response – Most user simulations to date have involved single responder simulation models. Fully automatic devices, that may be deployed in a public access program or used in systems where there are 2 or more responders, must be analyzed for use in multi-person bystander/responder scenarios for safety. Furthermore, environmental conditions in which the automatic shock delivery may be used may be compromised, such as excess noise and activity, should be addressed.
3. Manufacturers should disclose how the automatic shock delivery system impacts ‘hands off time’ (time of ending CPR to delivering a shock) since recent literature suggests the time from ending CPR to shock delivery should be minimized for the best chance of successful defibrillation.^{xi}

4. Automatic delivery systems rely solely on the AED's assessment of the patient environment, therefore data should be presented as to why the automatic delivery system remains safe for both operators and bystanders.

On balance, the risks associated with a fully automatic system should be justified against the benefits. User groups should be identified and data should be provided that accurately assess the incremental hazards. Usability data should be supported with data and provided in the submission. Consideration is necessary of the risks associated with introducing mixed fleets of defibrillators into public spaces and the expectations that users may have when encountering a fully automated device. Labeling and warnings on fully automatic defibrillator should be very clear – such that bystanders and responders know that the device is going to be delivering a shock on its own.

4. Post Market Study

Because there are differences in implementation of design and device performance among manufacturers, a post market study plan should be submitted with each 510(k) by each manufacturer when introducing an AED that impacts patient care for the first time. The study plan should include a justification of the sample size, study endpoints and the strategy for identifying any new safety or performance issues.

ENDNOTES

ⁱ Dated October 28, 2003

ⁱⁱ Kerber, R. et al. Automatic External Defibrillators for Public Access Defibrillators: Recommendations for Specifying and Reporting Arrhythmia Analysis Algorithm Performance, Incorporating New Waveforms and Enhancing Safety. *Circulation*. 1997;95:1677-1682.

ⁱⁱⁱ Page 9.

^{iv} Dated April 1999.

^v 21 CFR 820.30(g)

^{vi} Dated December 1996.

^{vii} Dated April 19, 2001.

^{viii} Dated August 1993.

^{ix} Snyder, DE et al. External series resistors accurately model waveform time course, but not cardiac dose in animal models of defibrillation. *Resuscitation*. 2003;56:238 (abstract).

^x 21 CFR 58.

^{xi} Yu, T et al. Adverse outcomes of interrupted precordial compressions during automated defibrillation. *Circulation*.2002;106:368-72.

Eftestol, T et al. Effects of interrupting precordial compressions in the calculated probability of defibrillation success during out-of-hospital cardiac arrest. *Circulation*.2002;105:2270-3.