SUMMARY MINUTES

MEETING OF THE CIRCULATORY SYSTEM DEVICES ADVISORY PANEL

OPEN SESSION

July 28 and 29, 2004

Gaithersburg Holiday Inn

Gaithersburg, MD

Circulatory System Devices Advisory Panel Meeting
July 28, 2004

Attendees

Chairperson
Warren K. Laskey, M.D.
Uniformed Services University of the Health Sciences

Voting Members
Mitchell Krucoff, M.D.
Duke University Medical Center

William H. Maisel, M.D., M.P.H.
Brigham & Women's Hospital

Sharon-Lise Normand, Ph.D.
Harvard School of Public Health

Consultants
Jeffrey A. Brinker, M.D.
Johns Hopkins Hospital

Normal S. Kato, M.D.
Cardiac Care Medical Group

John C. Somberg, M.D.
American Institute of Therapeutics

Albert L. Waldo, M.D.
University Hospital of Cleveland

Clyde Yancy, M.D.
University of Texas Southwestern Medical Center

Industry Representative
Michael Morton
Cardiac Surgery, North America Sorin Group

Consumer Representative
Christine Moore
Baltimore, MD

Food and Drug Administration
Bram Zuckerman, M.D.
Director
Division of Cardiovascular Devices

Geretta Wood
Executive Secretary

Scott Proestel, Ph.D.
Office of Device Evaluation

Barbara Krasnicka, Ph.D.
Office of Surveillance and Biometrics

Owen P. Faris, Ph.D.
Office of Device Evaluation

CALL TO ORDER

Panel Chair Warren K. Laskey, M.D., called the meeting to order at 9:01 a.m. **Panel Executive Secretary Geretta Wood** read the conflict of interest statement. Full waivers had been granted for Drs. Brinker, Krucoff, Maisel, Somberg, and Waldo for their interests in firms that could be affected by the recommendations of the panel. The Agency took into consideration certain matters concerning Drs. Brinker, Krucoff, and Yancy, who reported past or current interests involving firms at issue but in matters not related to the day's agenda. Ms. Wood noted that Dr. Laskey had consented to serve as chair for the duration of the meeting. Dr. Laskey then asked the panel members to introduce themselves. Dr. Waldo participated by speakerphone.

Ms. Wood then read the appointment to temporary voting status. Drs. Laskey, Brinker, Kato, Somberg, Yancy, and Waldo had been appointed voting members for the duration of the meeting.

OPEN PUBLIC HEARING

Dr. Laskey read the Agency's statement on transparency of the device approval process. No comments were made.

SPONSOR PRESENTATION

Arthur Feldman, M.D., Ph.D., Jefferson Medical College, Philadelphia, and co-chair of the COMPANION trial, provided an overview of the sponsor's presentation and introduced the sponsor's speakers and consultants. He presented the regulatory history of the Guidant cardiac resynchronization therapy defibrillator (CRT-D) and noted that numerous communications between the sponsor and FDA took place during the COMPANION trial. For

this PMA submission, which seeks expanded indications and claims for the sponsor's CRT-D devices, the sponsor submitted all adverse events for CRT-D and performed a system safety analysis, even though CRT-D safety has been previously established.

In up to 30 percent of cases, heart failure is associated with prolonged conduction, resulting in a dysynchronous contraction and further impairment of myocardial function. Drugs cannot address this problem. Resynchronization through electrical stimulation of both ventricles improves myocardial function and reverses ventricular remodeling. CRT-D therapy corrects the hemodynamic abnormalities that result from a delayed activation of the left ventricle.

CRT-P or CRT-D devices have the potential to reduce mortality and heart failure hospitalizations in patients with advanced heart failure. No appropriately powered clinical trials designed on an intent-to-treat (ITT) basis have prospectively investigated the effect of CRT on mortality or hospitalization. The COMPANION trial was designed to determine whether CRT with biventricular pacing only (CRT-P) or CRT with both biventricular pacing and defibrillation (CRT-D) resulted in a significant reduction in a composite endpoint consisting of time to first all-cause hospitalization or all-cause mortality compared with optimal pharmacological therapy (OPT) alone. The motivation behind using a composite endpoint was the desire to address both mortality and morbidity. Incorporating all-cause hospitalization into a composite endpoint helps address the challenge of competing risk and raises the bar for demonstrating CRT effectiveness.

The study consisted of three groups of patients randomized to OPT, OPT + CRT-P, or OPT + CRT-D. The clock began running at the time of randomization. Any event was considered a trial endpoint, even if the device not yet implanted. The OPT + CRT-D group is the focus of Guidant's FDA submission. Guidant proposed to expand the current implantable cardiac device (ICD) indications for CRT-D to include the COMPANION patient population criteria.

The primary endpoint was a composite of death from any cause and hospitalization for any cause (which included intravenous inotropes or vasoactive drugs administered for more than 4 hours in any setting). The composite primary endpoint included mortality to account for mortality as a competing risk. It was analyzed as time to first event as measured from the randomization visit; ITT analysis started at the time of randomization, prior to device implant. By agreement with FDA, and to preserve hospitalization as a valid morbid clinical endpoint, hospitalization associated with the investigational device implant was not considered a hospitalization event. Secondary endpoints consisted of all-cause mortality and cardiac morbidity.

Inclusion criteria consisted of NYHA Class III or IV status; OPT (i.e., loop diuretics, beta blockers, ACE inhibitors, and spironolactone); left ventricular ejection fraction = 35 percent; left ventricular end diastolic dimension of = 60 mm; QRS = 120 ms and PR > 150 ms; heart failure hospitalization (or equivalent) between 1 and 12 months prior to enrollment; and no indication for a pacemaker or ICD. The study was powered to detect a 25 percent relative reduction in 12-month event rates in each device arm versus OPT for both primary and secondary endpoints. The power was greater than 90 percent for the primary endpoint. The trial was event driven and had a target number of 1,000 first events to detect the 25 percent reduction for the primary endpoint. The study was managed by several committees independent of the sponsor, including a Steering Committee, a Morbidity and Mortality (MM) Committee, and a Data and Safety Monitoring Board (DSMB). The DSMB performed sequential monitoring of primary and secondary endpoint events every 6 months.

Peter Carson, M.D., Associate Professor of Medicine, Georgetown University, summarized the data handling and adjudication process and reviewed the definitions used in the

study, including hospitalization event, cause-specific mortality, and cause-specific hospitalization; preoperative, perioperative, and postoperative mortality; hospitalization classifications; and cardiac morbidity. He also described the mode-of-death analysis. The sponsor made it a point to use definitions that had been used in other clinical trials.

The MM Committee did not screen adverse events; it reviewed source documentation from investigator sites that was provided by the CRO, including hospitalization and death data. A primary and secondary reviewer were assigned to each event. The MM Committee was not blinded but functioned in equipoise regarding the study hypothesis; therefore, the knowledge of the treatment arm should not have influenced adjudication. The committee at no time had knowledge of cumulative events or assembled data. CRO members were present at committee meetings, but no sponsor representatives were ever present, and all communication was sent to the CRO or to the Steering Committee.

The MM Committee believed that the protocol intended that an event be sufficiently morbid to enter into a composite endpoint with death. Therefore, a 24-hour duration was initially selected as the descriptor of an all-cause hospital admission. However, early in the adjudication process, it became apparent that discharge times were not uniformly available. Therefore, the committee agreed to adopt the more verifiable and precise approach of a "calendar date change." The change was approved by the Steering Committee and used for all hospitalizations and included in all analyses. A total of 113 hospitalizations were adjudicated before adoption of this criterion; all were reviewed, and none were changed.

The MM Committee used the protocol-defined cardiac morbidity definition of the use of IV inotropic/vasoactive medication in an OPT setting to treat decompensated heart failure. This

definition ensured that administration of IV therapy was clinically meaningful. A follow-up case report form (CRF) was used to collect IV infusion data for the primary endpoint.

The COMPANION Endpoint Committee provided operational criteria for events occurring during the study. The classifications were those used in previous heart failure clinical trials. They provided verifiable data and maximized capture of significant events. The adjudication process consisted of activities that are standard practice for clinical trials related to heart failure.

Michael Bristow, M.D., Ph.D., presented the effectiveness results. The study involved 120 U.S. centers, averaging 12 patients per center. None of the baseline demographic parameters varied between the two treatment groups. The patients' average age was in the late 60s, which is a bit older than in most heart failure trials, and the study involved more women than most heart failure trials do. Enrollment ended in November 2002.

Kaplan-Meier curves show that the 12-month event rate in the OPT group was 68 percent, higher than projected. For the primary endpoint of all-cause mortality or all-cause hospitalization, the event rate in the CRT-D group was 56 percent. The hazard ratio was .80, and the difference between the CRT-D and OPT groups was statistically significant. For the CRT-P group, the outcomes were virtually identical to those of the CRT-D group. In the subgroup analysis, all point estimates were to the left of unity, indicating homogeneity of effect for the primary endpoint. Outcomes were similar for the secondary endpoint of all-cause mortality.

The sponsor's cardiac morbidity assessment was designed as an index to encompass all significant events that could happen to a heart failure patient, including serious device-related hospitalization. No standard definition exists for cardiac morbidity for advanced heart failure trials, so the protocol defined cardiac morbidity for the COMPANION trial. The endpoint was

intended to measure frequency and duration of all cardiac morbid events as defined in the protocol. CRT-D patients demonstrated significantly lower rates of cardiac morbidity than the OPT patients.

The sponsor faced several challenges in conducting the COMPANION trial. The trial had a 91 percent implant success rate but had to overcome the lack of therapy effect in patients with unsuccessful implants. In other words, the data analysis included patients who could not physically receive a device. Another challenge was that contemporaneous device therapies were approved while the study in progress, including several CRT-P and CRT-D devices, and indications for ICDs were expanded. These challenges slowed enrollment and made maintaining patients in the study somewhat of a challenge. Once the other devices were approved, enrollment started to drop. The investigators were faced with a difficult choice of treating OPT patients with CRT or maintaining them in the study. The Steering Committee recommended keeping the OPT patients in the study. If a patient had a heart failure hospitalization with objective documentation of progressive symptoms requiring IV treatment, it would be classified as an event and the patient would receive the appropriate market-released therapy.

As a result of the disproportionate withdrawal rate (13 percent in the OPT group and 2 percent in the CRT-D group), the independent statistician recommended obtaining vital status and hospitalization status on all withdrawn patients. The reconsent process created a major delay in data analysis. The sponsor concluded that the measures taken minimized the impact of withdrawals. In addition, the more complete data were not qualitatively different from censored data at withdrawal.

In summary, the patient demographics were well balanced across groups. There was a significant reduction of 20 percent in time to first all-cause mortality or all-cause

hospitalizations; a reduction of 36 percent in time to all-cause mortality, and reduction in frequency and duration of cardiac morbidity. The reconsent process minimized the potential for bias.

David DeMets, Ph.D., professor and chair, Department of Biostatistics and Medical Informatics, University of Wisconsin Medical School, a consultant to the sponsor, presented information on several statistical issues raised by FDA. He explained that Kaplan-Meier curves do not assume proportional hazards, and the latter are not required for the log rank test used by the sponsor. The log rank test uses the Cox proportional hazards model if the only covariate is treatment. Log rank has good statistical properties for stochastic ordering.

COMPANION, like many positive heart failure trials demonstrating benefit, showed consistency across all the standard primary and secondary endpoints. The log rank analysis is valid because proportionality of hazards is not required. A key requirement for use of the analysis—that the survival curves do not cross—was met. The bias from the informative censoring was resolved by postwithdrawal follow-up. The alpha allocation was appropriate and consistent with other trials. The subgroups, however, must be treated with extreme caution, if at all. The consistency of the trial results is impressive.

Leslie A. Saxon, MD, Professor of Medicine and director of cardiac electrophysiology, University of Southern California Medical Center, reviewed the sponsor's safety data. She noted that the device and the associated lead have been approved in a patient population with current indications for both CRT and an ICD. Adverse events were defined as any undesirable clinical event and were divided into complications and observations; the latter group consisted of events that were generally transient or reversible with noninvasive intervention. The sponsor evaluated system safety, device safety, and patient-related safety as

well as procedure-related adverse events. Dr. Saxon presented definitions for each type of safety and summarized results of the sponsor's analysis. System and device safety was consistent with or better than reported rates for CRT.

Finally, the sponsor presented the Steering Committee's responses to FDA's questions.

Panel Questions for Sponsor

Panel members asked for clarification as to whether multiple attempts to implant the device counted as hospitalizations and how that impact on the patient was incorporated into the sponsor's analysis; whether the sponsor had information on cumulative per patient hospitalizations; what the reasons for changing the definitions of the variables were; how the data flowed from the CRO to the sponsor and what the process was for communicating among the different committees as definitions evolved; and whether the withdrawal rate was related to adverse events. Sponsor representatives provided clarification.

FDA PRESENTATION

Owen P. Faris, Ph.D., Scientific Reviewer, listed the FDA reviewers and summarized the regulatory background of the device. He also summarized the formal agreements between FDA and the sponsor. The sponsor's proposed changes to the indication involve expanding the indication to include the entire population described in the COMPANION trial and new claims based on the primary composite endpoint and the secondary endpoint of mortality.

Barbara Krasnicka, Ph.D., FDA statistical reviewer, focused on problems connected with the study design, data quality, and statistical analyses. She reviewed the trial structure and noted that data quality is influenced by clear definitions of variables and methods used for data

collection, editing, and assessment. During the trial, the primary effectiveness endpoint was modified three times. The collection of hospitalization events was based only on admission and discharge dates, not exact time. The capture of hospitalization events longer than 4 hours during which patients received IV therapy was based on the duration of the IV therapy as recorded in the follow-up CRF. Because some hospitalization events did not have CRFs, some events may not have been captured.

In addition, some patients were followed up for only a few weeks or days after the trial stopped in 2002. The withdrawal rate was especially high in the OPT group; FDA is concerned that worsening of patients' health was the reason for many withdrawals. In addition, although the withdrawn patients were asked to consent again to the sponsor collecting endpoint data, FDA is concerned that the postwithdrawal information regarding hospitalizations may be unreliable.

The results of the sponsor's statistical analysis for the primary effectiveness endpoint may be problematic because the endpoint was redefined during the study. In addition, the assumptions required for the statistical methods use may not be met; the censoring mechanism applied may not be independent of the occurrence of the event or endpoint; and the hazard functions and the Schoenfeld residuals suggest that the proportionality assumption essential for the Cox model may not be valid. Statistical analyses for the all-cause mortality secondary endpoint raise similar concerns.

The sponsor considered only cardiac morbidity events that occurred in hospitals. However, some events took place outside hospitals; therefore, the data do not supply the full information on all cardiac morbidity events.

Under both worst- and best-case scenario analyses, the OPT patients experienced fewer adverse events in the 6 months following randomization. The sponsor's statistical analyses are of

concern because correlation between multiple events in a patient was ignored, timing of adverse events was not taken into account, and many lost-to-follow-up patients were excluded. Consequently, all exploratory analyses should be interpreted with caution. In summary, the treatment comparisons for the primary effectiveness and mortality endpoints should be interpreted with caution because of changes in the all-cause hospitalization definition, the fact that withdrawals were not clearly independent of outcome, and the open-label design created the opportunity for bias.

Scott Proestel, Medical Officer, presented the Agency's clinical review of the COMPANION trial. He summarized the trial design, discussed issues concerning the primary and secondary endpoints, provided additional efficacy analyses, and reviewed the results of the safety analysis. Although the CRT-D and OPT cohorts were well matched for age and gender, there was a modestly higher proportion of Class IV and ischemic patients in the OPT arm. Mortality in Class IV subjects was 2.9 times higher than in Class III patients and 1.7 times higher in ischemic patients than in nonischemic patients. Both imbalances favored the device arm.

Dr. Proestel reviewed the changes to the primary endpoint and noted that a compelling explanation would have been that the new definition was somehow inherent to the old, meaning that to be hospitalized necessarily meant staying in the hospital overnight. That was not the case. If that were true, the clarification should not have been necessary. Far from adding clarity, the requirement of a minimum duration makes the definition more complicated. The definition is considerably more narrow than the encompassing claim of "all-cause mortality plus all-cause hospitalization." Moreover, events that were not hospitalizations were considered as such for the purpose of the primary endpoint. The changes in the endpoint are of concern to the Agency

because doing so would allow for the possibility of modifying the endpoint in such a way as to favor the device arm.

The definition of cardiac morbidity did not match the definition provided in the protocol. The definition instead consisted of any hospitalization during which one or more of the specified "cardiac morbid" events occurred. Thus, a single hospitalization that had multiple cardiac morbid events would only count once toward the endpoint. FDA does not have the data to calculate results for the original endpoint specified.

Patients in the device arm of the COMPANION trial did not experience a decrease in hospitalizations. FDA performed a calculation for the all-cause hospitalization rate, which was not specified in the protocol. The CRT-D arm had a mean of 2 hospitalizations per year, and the OPT arm had a mean of 1.6 hospitalizations per year. In addition, implant hospitalization is not a single, nonrecurring event; all device subjects will have to be hospitalized again to have the device replaced due to battery depletion. Even if one believes that implant hospitalizations were recurring, but at a trivial rate, the rate was greater than for cholecystectomy, which was included as a hospitalization. The encompassing claim of all-cause hospitalization, by its nature, includes events that may not be tightly linked to the action of the device; excluding the implant attempt because it does not characterize the effect of the device thus does not make sense. Even if one ignores the implant hospitalizations, the effect of the device on hospitalizations was not of sufficient magnitude during the trial to even account for the implant hospitalizations that were required to obtain the device. FDA is not advocating a change in the primary endpoint, but is simply arguing that the additional analysis of all-cause hospitalization is reasonable and clinically relevant.

FDA reviewed all adverse events that occurred during the trial. The adverse events in the device arm were not of a rate or severity beyond what might be expected; in fact, the proportion of adverse events that were complications was actually lower in the device arm.

Dr. Faris summarized the Agency's conclusions. With regard to the primary endpoint, modifications were made to the hospitalization definition during the trial. Fundamental statistical assumptions underlying some analyses may not have been met. Whether COMPANION demonstrated a benefit for the primary endpoint as originally defined is unknown. With regard to the secondary endpoint of mortality, the CRT-D device was associated with a decrease in all-cause mortality compared with OPT. In addition, the sponsor's analyses included data obtained from patients after withdrawal. When implant hospitalizations were included, the CRT-D device was associated with an increase in all-cause hospitalizations and an increase in adverse events compared with OPT.

Panel Questions for FDA

Panel questions focused on obtaining clarification on the problems the Agency found with the sponsor's statistical analysis and the impact of the changes in hospitalization definition.

PANEL DISCUSSION

William H. Maisel, M.D., M.P.H., Panel Reviewer, focused on hospitalizations, withdrawals, the mortality endpoint, and safety. He asked for clarification on what prompted the redefinition of the hospitalization endpoint. In his opinion, the sponsor did not clarify matters by changing it. He also asked the sponsor to clarify the timing of event adjudication as it related to

data analysis to verify that no statistical analysis was performed before the change in hospitalization definition.

Dr. Maisel noted that it was foreseeable that there would be a large number of withdrawals because doctors would have to withdraw patients in order to treat them properly. The sponsor did a commendable job of tracking down data for withdrawn patients, although the methodology raises some questions about the validity of the information.

The devices do result in improved survival and decreased mortality. The evidence indicates that the device improves heart failure symptoms, but the data on hospitalization are less convincing. However, the primary safety outcomes do not include data on attempted implants.

Panel members asked questions about deaths not related to the device; frequency of device firing in the CRT-D group; reasons for the higher rates of sudden cardiac events in the CRT-P group; the impact of medication changes on hospitalization rates in all groups; differences in length of hospital stay in the groups; effects of withdrawals; and randomization methods and blinding issues.

Many panel members had concerns about the sponsor's statistical analysis. Several members expressed concern that the changes in definitions during the trial were driven by awareness of the data; however, the sponsor assured the panel that that was not the case. Other panel members, however, felt that the definitional changes did not substantively affect the final analysis, although many felt that the hospitalization endpoint had been clouded by the changes. One panel member felt that the data indicate a high risk of complication. A comparison to ICD devices without pacing would have been helpful.

FDA QUESTIONS FOR PANEL

1. **Please comment on whether modifications to the hospitalization definition impact the interpretation of the primary endpoint.**

The panel did not have consensus in answering this question. Some panel members felt that the modifications probably did not adversely affect the primary endpoint efficacy determination. However, they were displeased with the incomplete information on hospitalization. Substantial problems exist with the hospitalization redefinitions, but looking at absolute mortality, the other secondary endpoints, and hospitalization, all the results seem to be going in the same direction. Other panel members felt that changing the definition, the potential for analysis of data prior to adjudication, and the large number of withdrawals all affected the interpretation of the endpoint. Although the analysis presented was not persuasive enough to modify the clinical sense that the endpoint was met, this study was not a model for conducting a clinical trial.

2. **Please comment on the impact of modifications to the hospitalization definition on the interpretation of the secondary endpoint of mortality.**

Panel members felt that mortality was not affected. Because of the competing risks, it is difficult to strictly analyze hospitalization in that context.

3. **Are the data from the COMPANION clinical trial sufficient to support an expanded patient population for the sponsor's CRT-D devices?**

The panel concurred that the data are sufficient to support an expanded patient population for the CRT-D devices.

4a. **With respect to statements in the Indications for Use regarding the primary endpoint, are the data from COMPANION sufficient to support claims based upon the primary endpoint results?**

The panel was not in consensus. The data are clearly limited in addressing the all-cause hospitalization issue.

4b. With respect to statements in the Indications for Use regarding the primary endpoint, are the data from COMPANION sufficient to support claims based upon the primary endpoint results? If so, please comment on whether the language of the proposed Indications for Use statement adequately describes this endpoint. In particular, please discuss whether the term "all-cause hospitalization" is appropriate.

The panel felt that it had answered the question earlier; it was not in consensus as to the answer.

5. With respect to statements in the Indications for Use regarding the secondary endpoint of mortality, are the results from the COMPANION clinical trial sufficient to support a mortality benefit claim for the sponsor's CRT-D devices in the COMPANION population?

The panel agreed that the results from the trial are sufficient to support a mortality benefit claim for the device.

6a. Please comment on whether the CRT-D labeling should characterize the total number of hospitalizations and length of time patients spent in the hospital for the CRT-D and OPT arms of the COMPANION trial. 6b. If so, please comment on whether device implant hospitalizations should be included as part of that analysis.

The panel was not in consensus. Many panel members thought it would be an arduous amount of work to add the information to the label and were not sure that doing so would provide meaningful information. Because panel members were not completely comfortable with the data, it would be inconsistent to quantitate it and put it in the label. The labeling should note that the device reduced risk of all-cause hospitalization, heart failure symptoms, and postimplant hospitalization, but did not necessarily reduce total hospitalization rates.

Although most panel members felt that the data on implant hospitalizations should be included in the labeling in addition to the total number of hospitalizations and length of time patients spent in the hospital, there was not consensus.

Some panel members felt that including the statement on all-cause mortality in the indications was inappropriate. It was suggested that a bullet be added to the definition of hospitalization that captures the panel's concern about rehospitalizations and replacements.

Another panel member suggested a separate table on events surrounding primary implantation.

Panel members noted that to some extent, hospitalizations are physician dependent.

7. Please comment on whether the CRT-D labeling should present adverse events from the CRT-D and OPT arms of the COMPANION trial in a consolidated manner that would allow their comparison.

Although panel members wanted to see adverse events from both arms provided, many panel members felt that presenting the information in a consolidated manner would potentially be misleading.

8. Please comment on whether data obtained from patients after withdrawal should be used in any of the analyses described in the device labeling.

The panel concurred that the data obtained following withdrawal should be used in the analyses.

OPEN PUBLIC HEARING

No comments were made.

VOTE

Executive Secretary Wood read the voting options. The panel voted unanimously that the device was approvable with the following conditions:

1. The instructions for use should be amended to remove the language referring to all-cause hospitalization and simply refer to all-cause mortality and improvement in symptoms.
2. The labeling should include a separate statement about the hospitalization experience in the clinical trial, along with the appropriate explanatory language and caveats, that captures the panel's concerns.

POLL

In voting to approve the device, many panel members noted their concerns about the hospitalization data. Several panel members noted that they were voting reluctantly for approval, in part because the labeling suggests that the primary endpoint was mortality. The way the study defined all-cause hospitalization does not reflect a real-world interpretation of the variable.

ADJOURNMENT

Dr. Laskey thanked the participants and adjourned the meeting at 5:24 p.m.

Circulatory System Devices Advisory Panel Meeting
July 29, 2004

Attendees

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Geretta Wood
Executive Secretary

Oscar H. Tovar, M.D.
Medical Officer
Office of Surveillance and Biometrics

Beverly Gallauresi, RN, MPH
Office of Surveillance and Biometrics

CALL TO ORDER

Panel Chair Warren K. Laskey, M.D., called the meeting to order at 9:04 a.m. **Panel Executive Secretary Geretta Wood** read the conflict of interest statement. Full waivers had been granted for Drs. Krucoff and Ornato for their interests in firms that could be affected by the recommendations of the panel. The Agency took into consideration certain matters concerning Drs. Krucoff, Maisel, Ornato, Ringel, and Somberg, who reported past or current interests involving firms at issue but in matters not related to the day's agenda. Ms. Wood noted that Dr. Laskey had consented to serve as chair for the duration of the meeting. Dr. Laskey then asked the panel members to introduce themselves.

Ms. Wood read the appointment to temporary voting status. Drs. Laskey, Kato, Ornato, Ringel, Somberg, and Vetrovec had been appointed voting members for the duration of the meeting.

FDA PRESENTATION

Beverly Gallauresi, RN, MPH, OSB, presented a summary of adverse events reported with automatic external defibrillators (AEDs). She described the medical device reporting (MDR) system and defined adverse events. She then described the Manufacturer and User Facility Device Experience (MAUDE) system and the methodology for retrieving device reports on AEDs from the MAUDE database. Her research involved a detailed assessment of reports received from August 1996 through December 2003. A total of 7,644 adverse event reports were submitted during the period: 590 deaths, 10 injuries, and 7,044 malfunctions. One limitation of data from the MDR system is that events represent a subset of the current total; the system also suffers from underreporting, a lack of incidence data, biased reporting, and uncertain causality.

Oscar H. Tovar, M.D., Medical Officer, presented a descriptive analysis of the reports received on AEDs. The benefits of early defibrillation in public places have been shown in numerous studies. The estimated rate of growth in AED deployment is expected to be about 20 percent per year for next 5 years; 150,000 devices are expected to be shipped in 2005. The success of early defibrillation implies that AEDs work in the first attempt and work consistently in any subsequent attempts. A failure to deliver a shock significantly decreases the probability of survival of a patient in ventricular fibrillation (VF). Information on adverse events involving AEDs is scarce.

In the Agency's review MDRs submitted by AED manufacturers for AED-related adverse events, the manufacturer results and conclusion codes were used to assess the association of device and component failure with patient death. The early years—1996 to 1999—were analyzed separately from later years because the technology changed. In early years, 191 deaths, 1,579 malfunctions, 6 injuries, and 17 other events were reported. In later years, 399 deaths, 5,465 malfunctions, 4 injuries, and 21 other events were reported. The malfunctions and deaths increased in the later period, but one must take into account the increasing number of AEDs on the market. The ratio of deaths to malfunctions was 10 percent for the early period and 7 percent for the later period. Some malfunctions occur during self-diagnostics. Few injuries occurred each year; the maximum was 3 (in 1996 and 2001). In 2001, there was an increase of 100 deaths, probably due to an increase in AED numbers. Twenty-six manufacturers reported during this period. This is a retrospective, descriptive analysis because of the absence of an accurate denominator. Even if the Agency knew the number of AEDs deployed, one would have to look at the data with caution.

The results suggest that the number of reported deaths associated with AED failure is markedly more frequent than injuries. The number of reported AED failures is increasing along with the number of deployed AEDs. There has been a relative decrease in reported electrical component failure and in reported device operation outside specification. The increase in the number of reported deaths over time associated with AEDs may have several contributing factors, including device availability.

Panel members asked brief clarifying questions. Dr. Tovar noted that many malfunctions occur during self-test, not during use. In response to a panel member's question, he replied that it is often not possible to determine whether a patient in VF would have survived if the device had not malfunctioned.

OPEN PUBLIC HEARING

Dr. Laskey read the Agency's statement on transparency of the device approval process.

Mickey Eisenberg, M.D., Ph.D., Professor of Medicine, University of Washington, noted that 80 percent of cardiac arrests occur in the home and that ventricular defibrillation is the only treatment for VF; if treated soon enough, 75 percent of patients survive. AEDs are safe and effective. Widespread dissemination of AEDs offers a chance to improve the mortality statistics. Society has taken a medical approach to sudden cardiac arrest (SCA) from VF; the costs are high, and research is limited. A consumer approach makes more sense now because the devices are safe and training is simple. Over-the-counter (OTC) approval for AEDs will drive down prices and make the devices more available. A consumer approach will save lives.

Kelli Harris, Lake Oswego, CA, had SCA when she was 27. She now has an implantable defibrillator. The prescription requirement impeded her ability to quickly get an

AED for other family members who might be prone to the same heart problem she has. AEDs are basic safety equipment, like fire extinguishers. They cannot hurt anyone and only emit a shock if there is a shockable rhythm. Children and adults can easily learn to use them. SCA can happen to anyone.

Robert E. O'Connor, M.D., M.P.H., president-elect, National Association of EMS Physicians, read the organization's position paper. He reviewed epidemiologic data on sudden cardiac death (SCD) and emphasized that many people who suffer SCD can be successfully resuscitated if certain critical actions such as 911 access, bystander cardiopulmonary resuscitation (CPR), rapid defibrillation, and prehospital advanced life support are accomplished in a timely and effective manner. Rapid defibrillation is the most critical of these interventions, and strategies to enhance survival should focus on reducing the interval from collapse to defibrillation. AEDs must be deployed quickly; integration of AED programs into emergency response systems is important. The association supports removal of the prescription requirement for AEDs. Because providing wider access to AEDs could delay calls to 911 for help, it is important that the devices themselves foster integration with 911 systems. The devices must be located in immediately recognizable and accessible locations.

Matt McKey, Director, Regulatory Affairs, Cardiac Science, Inc., Minnetonka, MN, spoke in support of AEDs. Because most SCA events occur in homes, easier access will improve survival rates of victims. If the panel recommends OTC status for AEDs, cardiac science calls for FDA to implement the least burdensome approach for manufacturers to gain 510k clearance: that is, issuing a guidance document within 30 days that allows the simple modification of labeling to remove "on the order of physician prescription" language. An alternative would be to allow a special 30-day 510k vehicle for modification of labeling. The devices are classified as

Class III and should be Class II; otherwise, if the devices are approved for OTC use, the integrity of the regulatory classification scheme will be compromised.

Richard A. Lazar, Esq., Chief Executive Officer, Early Defibrillation Law and Policy Center, presented basic epidemiologic information on SCA. Rapid defibrillation with AEDs is safe and effective. The devices are being promptly and properly used by variety of users in a variety of venues. Widespread deployment is a public health solution that will save thousands of lives. The prescription requirement currently in place adds an unnecessary layer to the purchase process. The perceived benefits of the prescription model do not transfer to a public access AED environment. Unlike drug interactions, SCA is binary from a public health perspective—people live or die. The only variable we can affect is the promptness with which defibrillation occurs. This policy change would not cost the government any money.

Geretta Wood read into the record a statement from **Donald J. Gordon, Ph.D., M.D., Chairman, Advisory Council on First Aid and Safety, American Red Cross,** consisting of the American Red Cross position statement on OTC AEDs. The Red Cross advocates OTC status for AEDs. A properly trained person and an AED are key to providing the best care to a cardiac arrest victim until emergency medical personnel arrive. Removing barriers to public access to AEDs and training more people could improve public response to unexpected cardiac events. If removal of this barrier results in even a 5 percent decrease in the number of lives lost each year, approximately 25,000 lives would be saved each year.

Frank J. Poliafico, R.N., Executive Director, AED Instructor Foundation, spoke in support of training for the users of AEDs. AEDs do not save lives—AED programs save lives. Public facilities need an onsite emergency preparedness plan that involves training and oversight. 15 million people are trained in CPR, but less than 5 percent of time, someone is doing CPR

when emergency responders arrive. Removing the prescription requirement does nothing to help the AED program issue; people need guidance and involvement from emergency medical services (EMS), or AEDs will not fulfill their promise of preventing deaths.

SPONSOR PRESENTATION

Carl Morgan, Co-Founder of Heartstream, introduced the sponsor's presentation. The sponsor proposes to remove the prescription requirement for the Philips HeartStart Home Defibrillator. The device has an established history of safe use, and the device can be used safely and for its intended purpose based on its labeling alone; it is therefore appropriate to remove the prescription requirement.

David Snyder, director of Research, Philips, presented an overview of the product and its regulatory history. The device is indicated for use with patients who are unresponsive or not breathing normally; if in doubt, the user should apply the pads. The user does not need to assess whether the patient is in cardiac arrest; the device will assess whether the heart is in a shockable rhythm. Mr. Snyder demonstrated use of the device, pointing out that the device has several reminders to call 911 and alert EMS. The device walks the user through administering the shock, then talks him or her through CPR. Once the user completes the initial sequence of CPR, he or she is instructed to stop; the machine analyzes the patient again and delivers a shock if necessary. The voice coaching reinforces CPR skills but is not intended to teach them. The pacing of prompts is methodical, but if the person goes quickly, the device prompts will catch up with him or her.

AEDs should be seen as safety equipment rather than medical equipment. The product was designed as safety equipment; he noted that the labeling urges the user to talk to his or her

doctor about health concerns or existing medical conditions. A large cohort of asymptomatic patients exists. The device is intended to be used once in a lifetime. As a result, it must be safe, ready to use when needed, and easy to use in the moment.

The device has core technologies that are common to other Philips defibrillator products. Earlier products had ECG displays and manual override capability. These were deemed inappropriate for the lay market and were replaced by enhanced prompting on pad placement, and additional CPR coaching. The device provides sophisticated arrhythmia detection. No single parameter can lead to "shock advised." Instead, multiple parameters are required: rapidity of signal conduction, ECG amplitude, heart rate, and stability of ECG complexes. Several studies have demonstrated the device's sensitivity and specificity.

More than 150,000 AEDs have been deployed since 1996, involving more than 1 million total patient applications. About 200,000 patients required shocks; 800,000 did not. The data are from nonrandom sampling based on ForeRunner AEDs. Philips has seen six confirmed AED use failures across its installed base. Four failures had no patient impact; one resulted in indeterminate patient impact; and one had patient impact, which has been filed as MDR. The top three causes of MDRs from this line of products are no voice prompts, poor patient-pads connection, and problems with algorithm sensitivity; those problems have been resolved.

The Philips defibrillators have a 40 percent market share and are responsible for less than 1 percent of filed MDRs. The first year annualized failure rate for HeartStart is 0.04 percent (of 8,170 devices deployed). The device performs various automated self-tests on a daily, weekly, and monthly basis. The design process has been iterative, and Philips has resolved various problems with each new model.

Philips provides extensive consumer support for the product, and the packaging includes information on SCA. Setup and maintenance steps include voice prompts.

Lance Becker, Professor of Medicine, University of Chicago, consultant to Philips, presented a clinical overview and discussed the safety and usability study. He reviewed epidemiologic data on SCA and outlined the "chain of survival" described by the American Heart Association. SCA survival in the home is worse than in public places. Most victims have no prior symptoms. The chain of survival specifies that patients should receive defibrillation within 5 minutes of collapse; in reality, it often happens more than 12 minutes after collapse, and that is cities with good EMS systems. Early access to defibrillation can save lives.

Data from early defibrillation programs (the American Airlines program, Chicago airport programs, and the casino security officers program) found no adverse events and good survival rates among patients who were defibrillated. Although two of those studies involved professional staff mandated to help, a study sponsored by the National Heart, Lung, and Blood Institute (NHLBI) provided compelling results that support the earlier findings. In the AED arm of that study, survival doubled. No serious adverse events were associated with AED use, and there were no instances of failure to call EMS. The study concluded that lay persons can use AED safely to provide early defibrillation.

The HeartStart safety and usability study was based on the worst case scenario—someone who had never seen the device and did not know how to do CPR. It tested two hypotheses: (1) that the HeartStart device (and the predecessor FR2 device) is safe even in the absence of training and (2) that the HeartStart and FR2 have high usability when used with primary labeling components plus a training video. The study used a mock cardiac arrest scenario with a fully dressed mannequin.

A total of 257 participants were randomized to either the FR2 device or the HeartStart device; approximately half of the participants in each group saw a training video. All participants were then asked to use the device on a mannequin in a mock cardiac arrest scenario.

The primary endpoints were safety and success. Safety was defined as no touching of the patient in a manner that could result in a shock across the rescuer's chest. Success was defined as shock delivered with pads positioned in a manner likely to defibrillate. Secondary endpoints were time to pads on and time to shock. Results for both groups of users demonstrated complete safety, but the video-trained users were more successful than naïve users. The video seemed to have a beneficial effect on time to shock and simulated use for Heart Start, but the outcome was not statistically different for both groups.

The results in the study were obtained under adverse conditions. Simulations cannot replicate every characteristic of real use, and it is unethical to subject volunteers to real stresses of such situations. Demographics were due to convenience, and real anatomy is more varied than would find on a mannequin. However, the study used state-of-the-art simulation methodology. The superior human characteristics of HeartStart home, suggest that the experience with the device will likely be better than with the FR2, which itself has been highly successful.

Mr. Snyder presented results from a labeling evaluation and simulated use study. The purpose of the study was to test the comprehension of secondary labeling materials for the HeartStart device. The labeling includes four components: an owners manual, a quick reference guide, a training video, and a quick start poster. The study also involved simulated use after review of only one component of labeling (the owners manual and the quick reference). Participants were recruited in 3 geographically diverse shopping malls. They had no medical or defibrillator training and had had no CPR training within 2 years. Participant ages ranged from

21 to 74. Participants were divided into four groups according to each labeling component and were tested on their comprehension of the materials; approximately 90 percent received a passing grade (70 percent of the questions correct). 178 of the 330 participants—those who read either the owner's manual or the quick reference—were randomized to a simulated use test. Primary and secondary endpoints were the same as in the safety and usability study. Those who only read the owner's manual did not achieve the predefined goal of 90 percent success, but those who read the quick reference achieved a 97 percent success rate. Results for other endpoints and the study limitations were similar to those of the usability study. All labeling was well understood, and the defibrillator was used safely in all cases.

As result of the study, the sponsor added information to the training video and the quick start poster about the intended use of the various labeling materials. The cover of the owner's manual was modified to clarify its purpose as a guide for setup and maintenance and a guide for accessories.

The sponsor conducted a lay user survey to determine whether lay use of Philips AEDs resulted in any previously unreported problems. A total of 78 homes and 1,645 businesses were surveyed. 13 percent of businesses had used the AED at least once to respond to suspected cardiac arrest. No harm or injury to users, bystanders, or patients resulted. No malfunctions or problems occurred, and all users were willing to use the device again. No safety or effectiveness issues were reported.

An ongoing HeartStart postmarket study will evaluate safety and effectiveness of lay use of the device. The sponsor proposes to extend the study to 200 home uses or 4 years from the date of OTC clearance. A DSMB will review the results annually and report them to FDA.

Jeremy Ruskin, M.D., Director, Cardiac Arrythmia Service, Massachusetts General Hospital, presented a clinical perspective. The profile of survivors is somewhat different from that of the subset of high-risk patients. Prior infarction was present in only about 50 percent of survivors. An undetected high-risk patient pool exists, representing a failure of the risk stratification schema. The first subset is beginning to be addressed from a prevention standpoint, but there is no current prevention strategy for the undetected group. Other safety equipment, such as smoke alarms, seat belts, and airbags, save many lives each year. Removing the prescription requirement would enable broad access to a safe and effective technology that is the only definitive treatment for SCA and would provide an opportunity to save some of the lives that would otherwise be lost to SCA.

The HeartStart is for the same intended user population and patient population as the prescription device. It has robust safety features, including an ECG analysis system, artifact detection, and no manual override. The device has an established history of safe use and can be used safely for its intended purpose based on its labeling alone. SCA is a major public health problem, and current survival rates are unacceptably low. A defibrillator is not a cure for the problem of SCA: As many as 40 percent of SCAs are likely to be unwitnessed, devices can be used incorrectly, and other factors can interfere with device deployment. Nevertheless, OTC AEDs represent a paradigm shift and a step toward wider access. Even a small impact could double current survival rates.

Panel Questions for the Sponsor

Panel members asked for additional information and clarification as to the estimated annual growth in AED deployment; safety of the device in wet environments, such as the pool or

beach; any populations that are not appropriate for the device; impact of AED use on people who already have an ICD; and performance characteristics of home use versus public use.

Several panel members expressed concern about pediatric use; although the device will be labeled for pediatric use, the sponsor presenters did not discuss issues related to that use. Separate pediatric and adult pads create the potential for confusion. Panel members suggested that if the adult pads can be used on children, only one set of pads should be provided. Moreover, most infant and child arrests are respiratory, not VF; use of home AEDs could delay appropriate respiratory care. The sponsor provided design validation data for pediatric use.

FDA PRESENTATION

Oscar H. Tovar, M.D., lead clinical reviewer, presented a brief summary of the regulatory history of the HeartStart device. He reviewed the regulatory context for removal of prescription labeling and noted that FDA's review focused on the device labeling and human factors evaluation. After reviewing the indications for use, he summarized the Agency's review.

The bulk of experience with AEDs is in public places, even though most SCAs occur at home. Cardiac function during VF deteriorates rapidly with time. This deterioration in function is associated with a rapid decrease in survival following VF-related SCA. A recent *JAMA* report proposed that if the duration of VF is less than 4 minutes, a defibrillation shock could be sufficient to convert VF to normal sinus rhythm. Between 4 and 10 minutes, CPR should precede defibrillation. After 10 minutes of VF, other measures such as cooling and controlled reperfusion are required. In the AHA chain of survival, CPR should precede defibrillation. The Philips AED allows shock within 4 minutes and CPR in the event of an unshockable or no rhythm. Survival rates and adverse events with AEDs have not been directly evaluated.

Human factors examines all aspects of a system's interface that are necessary for safe and effective use. Use includes the installation, calibration, operation, maintenance, repair, and disposal of the system or its components. Training and labeling are part of the user interface. In devices for emergency use, preparing a device and maintaining readiness are extremely important. Philips' usability testing covered some aspects of device setup and operation; it did not cover training, storage, or maintenance. The Agency's main concern over the user testing was that subjects were told that the mannequin was a simulated SCA victim.

FDA considers the Philips AED a tracked device. The sponsor proposes use of a registration card in conjunction with a database of shipment records. In case of a recall, multiple methods of notification will be used.

A postmarket study will follow-up with consumers after one year or after use of the device, whichever comes first. Its purpose is to assess safety and effectiveness after device use. It is tied to the customer reordering pads.

Uncertainty remains concerning the public's ability to safely use AEDs. The sponsor has presented data that characterizes human factors of the device and its labeling. However, survival rates and adverse events in home use have not been evaluated.

Panel Questions for FDA

Panel members asked the FDA reviewers whether they had identified a population that would be placed in jeopardy by use of this device; Dr. Tovar replied that such a population had not been identified. They also asked about the Agency's previous experience with removing the prescription requirement from a device. Megan Moynihan replied that the Agency's main experience has been with OTC diagnostic products such as glucose monitors.

PANEL DISCUSSION

William H. Maisel, M.D., M.P.H., Panel Reviewer, stated that AEDs effectively defibrillate the heart and restore it to normal. The studies on public access AEDs are impressive. He asked for more data on the reasons doctors have refused to provide AED prescriptions; sponsor representatives provided the data and noted that many doctors refuse to give prescriptions because they believe the patients do not need the device.

Dr. Maisel asked for clarification on aspects of device function, particularly the arrhythmia detection algorithm and the event review data management software. Sponsor representatives noted that only hospitals and other medical settings were permitted to use the software; it is not appropriate for lay users. Dr. Maisel expressed concern about possible delay in retrieving rhythm strips, but the sponsor noted that HeartStart is similar to all other AEDs in that regard. Dr. Maisel also asked for clarification as to the sponsor's rationale for not placing a "Call 911" sticker on the outside of the device; the timing of the CPR instructions; how the sponsor would deal with changes in guidelines for CPR and defibrillation administration; the notification process in the event of recall; and the expected life of the device and the role of the self-test in alerting the user to the product's expiration. Dr. Maisel noted that the sponsor has done a superb job in demonstrating safety and effectiveness. Although more information on the intended population would be useful, the benefits of removing the prescription requirement outweigh the risks.

Panel members noted that the prescription model does not apply to the situation with AEDs. They raised concerns about and asked for clarification on the use of the devices on people who have implanted devices; the inability to clearly define the target population; whether having a physician in the loop adds value; how to handle situations in which people do not want the

devices used on them for various reasons; reasons physicians denied prescriptions to patients seeking the devices; representativeness of the group participating in the usability studies; the sequence of using the AED and calling 911; the sponsor's plan for reaching purchasers in the event of recall or product updates; the sponsor's lack of data on storage and maintenance; and the opportunity for confusion created by the two-paddle design.

A panel member noted that neither the sponsor nor FDA could name a subpopulation that could be harmed by the device. Another panel member observed that respiratory issues tend to be more likely than heart problems among very young children and suggested that the product labeling include information on attending to ABC (airway, breathing, circulation) issues when dealing with an unconscious child. It was also noted that Federal and State legislation requires standardized training for use of defibrillators by EMS teams. The public needs to know that AEDs work because they buy time until EMS can arrive on the scene.

FDA QUESTIONS FOR PANEL

1a. Please comment on the adequacy of the testing that was performed to support the notion that lay users can safely and effectively use the product.

The panel concurred that Philips had done a commendable job to support the notion that users can safely and effectively use the product. However, the subject population may not be representative, and the maintenance aspect was not a focus of the research. Additional testing in a population that is more representative of the general population would be reassuring. Panel members suggested that the sponsor provide the device in languages other than English.

1b. Please comment on whether it is necessary to establish other aspects of usability . . . as a prerequisite for removing the prescription label.

Panel members concurred that the device adequately informs the user of its maintenance needs. They expressed some concern about the shelf life and concurred that more data on self-

testing, storage, and maintenance would be useful. The label should state explicitly what the shelf-life recommendations are. The self-test environment seems robust. Removing the prescription requirement does not significantly affect storage and maintenance.

2a. Please comment on the adequacy of the testing that was performed and the product labeling and training materials that are provided to support the notion that lay users would know *when* to use the product.

The panel concurred that the testing was well done, although the focus was on adult populations (both users and patients). Some subpopulations could be targeted for additional information.

2b. If you do not believe that the testing and/or labeling are adequate, please comment on the type of testing or labeling changes that would be necessary to support removal of the prescription label.

The panel concurred that the testing and labeling are adequate. Materials need to be included that emphasize "ABC" for infants and toddlers.

3a. Please comment on whether these recommendations regarding CPR are enough, or whether other measures are needed.

Panel members noted that the question was incorrect concerning AHA recommendations. The issue will be dealt with at the next guidelines conference. Early defibrillation is the best answer we have now. The real question is what to do with patients who are down for more than 12 minutes; none of the currently available AEDs deal with the problem. The only standard to which FDA can hold manufacturers is the current recommendation. The device is configurable to accommodate new guidelines. The panel recognized that the instructions for use may change as recommendations change. Panel members noted that for infants and toddlers, the documentation is not clear about the timing of CPR.

3b. Please comment on whether this concern is unique to an over-the-counter AED, or whether the same concern exists for the prescription version of the device.

The panel concurred that the same concern exists for the prescription version.

4. **Please comment on the adequacy of the external carton labeling in conveying important information to [lay users] that would allow them to know whether this product is right for them.**

Panel members suggested a variety of changes to the carton labeling that could clarify whether the potential user should purchase the product. Suggestions included stating that the device's prompts are in English; stating that the user should consult a doctor; indicating the risk of users of given ages needing the device; and listing what is needed to run the device (e.g., the physical capabilities required of the user, such as hearing). Panel members noted that the population at risk is not well delineated. The carton should state that the device is used to treat SCA victims who are nonresponsive and not breathing; it should say that it is an adjunct to care that will help patients until emergency responders arrive.

5. **Please commend on whether this testing is sufficient to remove the prescription-only label on the pediatric pads.**

The panel did not reach consensus on this question. Several members expressed concern about the small sample size in the sponsor's tests. Members discussed whether to include the pediatric pads with all devices, noting the possibility of inadvertent use of pediatric pads on adults. Many members felt that excluding pediatric pads would add an extra level of complication, but including both sets of pads in each unit creates potential for confusion.

6. **Please commend on the adequacy of [the sponsor's approach to prompting the user to activate the EMS system.**

Panel members felt that "Call 911" should be permanently written on the side of the device and should be in large, prominent lettering.

7. **Please comment on the adequacy of Philips' description of the methods they have in place to identify users in the event of a recall.**

Panel members concurred that the sponsor needs to maintain a detailed tracking system that follows consumers through the first point of sale. If protocols change, it is important to contact patients promptly. Because some devices will be purchased as gifts, the company must have end-user information.

8. Please comment on the adequacy of [the sopnsor's measures to encourage use of the MDR system].

Panel members said that putting the onus on the sponsor was burdensome. A built-in data gathering mechanism occurs when part replacements are ordered. It is not unreasonable to ask users to call an 800 number in the event of malfunction.

9. Please comment on the adequacy of [the sponsor's] proposal to collect information about the device used in the postmarket period.

The panel applauded the sponsor's postmarketing data collection effort. With a diligent effort by the sponsor, information on real-world use by people at different educational levels might be collected. To fill in more gaps would require a big clinical trial. It would be useful to collect information on effectiveness by demographic subgroups. It is also important to collect data on who does not respond to the sponsor's survey. Panel members also noted that the justification for the sample size is unclear and suggested that the study should focus on home use, not public access areas. Patient outcome data are critical.

OPEN PUBLIC HEARING

John Gregoire, Plano, TX, a survivor of SCA, spoke in support of eliminating the prescription requirement. He collapsed at his health club and was saved by a quick-acting fellow member (who was a heart surgeon) and the club's AED device. He has a home AED, but the prescription requirement was an impediment to getting it quickly.

Graham Nichol, M.D., chair, American Heart Association Task Force, said that the AHA endorses all efforts to reduce death and disablement from cardiac disease. Many events occur in the home, and most EMS personnel do not arrive quickly. An NLHBI-sponsored trial found significantly better survival, with few adverse events, for people who received AED. Lay AED users should receive training and information on maintenance.

Michael Willingham, Vice President, Regulatory Affairs, Medtronic Emergency Response Systems and Co-Chair of the American National Standards Committee for Performance and Safety of External Defibrillators, noted that Medtronic is a leading manufacturer of AEDs and defibrillators. The company encourages FDA to remove the prescription requirement for AEDs for certain models for lay users. Large-scale studies on AED effectiveness are encouraging. The nonprofit Emergency Care Research Institute issued a comprehensive report in June 2004 comparing AED models on the market and concluded that several models are appropriate for lay use. FDA authorization to market AEDs without a prescription would raise consumer confidence that the device is safe. In nearly all States, good samaritan laws cover the use of AEDs. All States require users to attend State-approved training; legislators and regulators should balance the need for these controls with public health considerations. Medtronic encourages FDA to develop a special controls guidance for AEDs.

Mary M. Newman, Executive Director, National Center for Early Defibrillation, stated that the center supports removal of the prescription requirement for AEDs. She cited statistics on SCA incidence and survival and emphasized that AEDs are safe, user-friendly devices. Changing the policy to allow OTC sales of AEDs would have a positive impact on SCA survival. Instructional materials must be comprehensive and user friendly. NCED is willing to collaborate with the FDA and manufacturers to develop such materials.

Geretta Wood read into the record a letter from **Carol J. Spizzirri, R.N., President and Founder, Save-a-Life Foundation,** stating that AEDs should be lower in cost and more available. They should be managed by the medical community so that users have appropriate training in their use and maintenance. It is important that good samaritan laws protect individuals who use AEDs.

Geretta Wood read into the record a letter from **Jack Grogan, a member of the Sudden Cardiac Arrest Survivor's Network.** He urged the FDA to drop the prescription requirement; anything that inhibits AED deployment is life threatening to future SCA victims.

Geretta Wood read into the record a letter from **Arthur L. Kellerman, M.D., M.P.H., Professor and Chair, Department of Emergency Medicine, Emory School of Medicine,** opposing the sponsor's submission. No evidence demonstrates that widespread deployment of AEDs in homes will save thousands of lives. Two studies suggest that in the areas under study, CPR, not AEDs, was responsible for improved survival following cardiac arrest. The American Airlines study trained more than 24,000 flight attendants and transported more than 70 million passengers but saved just 6 lives. No studies describe the benefit of home AED devices. The commercial imperative to sell AEDs has outpaced scientific research on the subject. The FDA does not have the data it needs to reach an informed conclusion one way or the other.

Richard L. Brown, president, Sudden Cardiac Arrest Survivor's Network, stated that his life was saved because of AED deployment and urged the FDA to remove the prescription requirement. SCA survivors are relatively young and represent a broad population. FDA's decision is important to the network's membership. As AEDs become more widely available, the price will drop. Removing the prescription requirement will have an immediate positive outcome in saving lives throughout the country.

Jim Baum, Lodi, CA, urged the panel to drop the prescription requirement for AEDs. An AED he purchased for home use saved his life.

Bill McNellis, Stuartsville, NJ, saved a colleague's life with an AED. The paramedics were able to download the information on the event from the device. AEDs should be made available to the general public, and the prescription requirement should be removed.

Consumer Representative Christine Moore noted her concerns about underserved populations' access to home AEDs. Because of the voice prompts, users at all education levels should understand how to use the devices. The box labeling needs improvement so that people know whether they should purchase the device.

ADJOURNMENT

Dr. Laskey thanked the participants and adjourned the meeting at 5:56 p.m.

I certify that I attended this meeting of the Circulatory System Devices Advisory Panel Meeting on July 28 and 29, 2004, and that these minutes accurately reflect what transpired.

_____
Geretta Wood
Executive Secretary

I approve the minutes of this meeting as recorded in this summary.

_____
Warren K. Laskey, M.D.
Chairperson

Summary prepared by
Caroline G. Polk
Polk Editorial Services
P.O. Box 2761
Charlottesville, VA 22902-2761
(202) 487-7867
cpolk@earthlink.net