

**SUMMARY MINUTES**

**OF THE**

**CIRCULATORY SYSTEM DEVICES**

**ADVISORY PANEL MEETING**

**OPEN SESSION**

**JUNE 19-20, 2000**

**Gaithersburg Hilton  
620 Perry Parkway  
Gaithersburg, MD**

**CIRCULATORY SYSTEM DEVICES ADVISORY PANEL MEETING****June 19, 2000****PANEL PARTICIPANTS****CHAIRPERSON**

Anne B. Curtis, M.D.  
University of Florida

**EXECUTIVE SECRETARY**

Megan Moynahan, M.S.  
Food and Drug Administration

**VOTING MEMBERS**

Michael D. Crittenden, M.D.  
Harvard University

Renee S. Hartz, M.D.  
Tulane Medical Center

Tony W. Simmons, M.D.  
Wake Forest University

**CONSULTANTS (Temporary Voting Status)**

Kent R. Bailey, Ph.D.  
Mayo Clinic

Michael J. Domanski, M.D.  
National Institutes of Health

Cynthia M. Tracy, M.D.  
Georgetown University Hospital

Melvin L. Griem, M.D.

University of Chicago

Minesh P. Mehta, M.D.  
University of Wisconsin--Madison

Alfred F. Parisi, M.D.  
Miriam Hospital and Brown University

Kenneth E. Najarian, M.D.  
University of Vermont College of Medicine

J. Frank Wilson, M.D.  
Medical College of Wisconsin

**Industry Representative**

Gary Jarvis  
St. Jude Medical

**Consumer Representative**

Robert A. Dacey  
Longmont, California

**Guest**

Robert L. Ayres  
U.S. Nuclear Regulatory Commission

**FOOD AND DRUG ADMINISTRATION**

James E. Dillard III  
Director, Division of Cardiovascular, Respiratory, and Neurological Devices

Brian E. Harvey, M.D.  
Chris M. Sloan  
John E. Stuhlmuller, M.D.  
Kimberly B. Peters  
Henry T. Heaton II  
Gary L. Kamer  
Marian S. Linde, R.N.

**OPEN SESSION—JUNE 19, 2000**

**Anne B. Curtis, M.D., Chairperson.** called the meeting to order at 10:05 a.m.

**Executive Secretary Megan Moynahan** read the conflict of interest statement, noting that waivers allowing full participation had been granted to Drs. Hartz and Parisi for their interests in firms potentially affected by the day's deliberations. Other matters concerning Drs. Curtis, Mehta, and Najarian were also considered but deemed unrelated and their full participation would be allowed. Ms. Moynahan read the appointment to temporary voting status for Drs. Bailey, Domanski, Tracy, Griem, Mehta, Parisi, Najarian, and Wilson. Panel Chairperson Dr. Curtis asked members of the panel to introduce themselves.

**OPEN PUBLIC HEARING**

There were no requests to address the panel.

**OPEN COMMITTEE DISCUSSION—PMA P990036 FOR CORDIS CORPORATION'S  
CHECKMATE SYSTEM****Sponsor Presentation**

**Dr. Dennis Donohoe, vice president for clinical research at Cordis,** gave the presentation overview. He discussed the problem of in-stent restenosis, noting that there are no effective therapies available, that the patient population is growing and experiences recurrent admissions, and that the pathology is well understood. Dr. Donohoe noted that radiation therapy has been used for about 100 years in treatment of malignancies and that there is a sizeable body

of knowledge about handling of radioactive sources and clinical response to benign hyperproliferative lesions. He discussed the selection of gamma radiation and the radiation procedure and described the source ribbons, catheter, and delivery device used. Dr. Donohoe stressed the team of experts used to ensure medical, radiation, and oncology expertise, and he also outlined the regulatory history of the device. He stated that the three randomized, double-blinded placebo controlled trials had shown overwhelming efficacy and durability of treatment in a difficult patient population with no alternative therapies and that risk was manageable by avoiding placement of new stents during the procedure and providing extended antiplatelet therapy.

**Dr. David R. Holmes, Jr., of the Mayo Clinic** gave the sponsor's clinical review. He discussed the mechanism and frequency of in-stent restenosis and gave specific case histories, as well as summarizing factors associated with in-stent restenosis and current treatment options. Clinical data were provided by three randomized, placebo-controlled, double-blind trials conducted with the Ir-192 radiation system, which were overseen by an independent safety board and angiographic core lab.

Dr. Holmes explained the evolution, design, and clinical demographic variables of the three trials, known as SCRIPPS I, WRIST, and GAMMA I. He also gave in-stent and in-lesion restenosis rates at six months and major adverse coronary events (MACE) for the SCRIPPS I and WRIST I trials, as well as similar data for the GAMMA I trial. In addition he described the

influence of lesion length and diabetes on in-lesion restenosis for the GAMMA I trial, and freedom from MACE at two years for the WRIST and GAMMA I trials. He concluded that the device showed concordant angiographic and clinical efficacy in all three studies, as well as durability and efficacy across a wide range of patient populations. On safety, Dr. Holmes reviewed a summary of all deaths in the three trials based on an intention to treat analysis and reviewed all individual deaths in the GAMMA I trial. In particular he analyzed myocardial infarctions (MIs) associated with late thrombosis in the GAMMA I trial. He noted that one death in the radiation group was possibly associated with late thrombosis and that there is an overall higher rate of MI in the radiation group because of the occurrence of late thrombosis. Dr. Holmes stated that long-term (three-year) angiographic follow-up in the SCRIPPS I trial showed no aneurysms or perforations. On radiation safety, he noted there had been no device failures, no Nuclear Regulatory Commission (NRC) reportable events, and no aborted procedures in the 1,000 patients treated to date.

**Dr. Richard Kuntz of Brigham and Women's Hospital** discussed specific clinical issues. He analyzed the issue of defining late total occlusions and late thrombosis, noting that late thrombosis is the most specific endpoint. He examined the GAMMA I trial results on late total occlusions and showed that a multivariate analysis of determinants for late thrombosis and late occlusions showed no significant predictors. Dr. Kuntz also examined the pooled data from all three trials, after justifying such pooling, which identified factors associated with late thrombosis

and allowed the hypothesis that it could be prevented by avoidance of new stent placement in conjunction with radiation. Dr. Kuntz also discussed the role of antiplatelet therapy in the prevention of late thrombosis by using prospective data from the SCRIPPS III registry and the WRIST Plus registry. He concluded that the rate of late thrombosis for radiation without new stent placement is comparable to placebo, that late thrombosis is largely confined to patients who received a new stent at time of radiation therapy, and that extended antiplatelet therapy helps prevent late thrombosis.

**Dr. Holmes** concluded that there is a major clinical need for the device and no alternative therapies. The device showed marked and concordant efficacy in all three trials in high-risk patients and showed durability over a two- to three-year follow-up. Safety was shown in over 1,000 procedures without a bailout or reportable event and through three-year angiographic follow-up that showed no radiation injury to vessels. Late thrombosis, which was an unanticipated event for the GAMMA I trial, is preventable by avoidance of new stent use and extended antiplatelet therapy. He concluded that risk could be managed through a warning in the labeling, a physician training program, and provision of updated information through postmarket surveillance.

#### **FDA Presentation**

**John E. Stuhlmuller, M.D.**, introduced the multidisciplinary FDA review team. He listed the four categories of the nonclinical evaluation: in vitro testing, biocompatibility testing,

animal testing, and source dosimetry, noting that most issues had been satisfactorily addressed. Sponsors have agreed in principle to revisions the FDA has requested on source dosimetry in the labeling.

The FDA clinical evaluation focused primarily on the SCRIPPS I feasibility trial and the GAMMA I pivotal efficacy trial, but included data from the WRIST, SCRIPPS-III, WRIST Plus, and pooled analysis. Dr. Stuhlmuller described the SCRIPPS I study, noting that 60 patients were enrolled and stratified into eight subgroups for analysis and followed at four to six months. He noted two cases of stent thrombosis and the resulting proposed lengthening of post-procedure anticoagulation from 14 days to eight weeks. Outstanding issues from the SCRIPPS report included the poolability of data across the subgroups and the interpretation of the pooled analysis of the six-month and three-year angiograms.

Dr. Stuhlmuller also described the GAMMA I study on 252 patients with angiographic and clinical follow-up at six and nine months. He described the study endpoints and noted that issues with the GAMMA I report included modification of definitions of myocardial infarction (MI) and target lesion revascularization (TLR) and duration of clinical follow-up.

On evaluation of safety and effectiveness, Dr. Stuhlmuller asked the panel to discuss how to evaluate study endpoints such as late total occlusion and late stent thrombosis and the edge effect, given the multiple definitions used during the studies. He summarized data from the

GAMMA I study on effectiveness, edge effect, safety, and clinical benefit versus risk and read the panel questions for discussion.

**Panel Clinical Review—Dr. Michael Domanski**

**Dr. Domanski** noted that the problem of in-stent restenosis is acute and there is no effective treatment. He raised a number of issues, including whether the device is safe and whether it prevents or reduces target lesion revascularization (TLR). For him, the central issue was that the device appears to reduce TLR, but more patients in the device group die or have a myocardial infarction. Dr. Domanski expressed other concerns over the poolability of data over the subgroups of patients and over the duration of time proposed. He was unsure that death and myocardial infarction statistics should be pooled and concerned about the low numbers and low power of the study, which prevent an analysis of death versus myocardial infarction incidence. He concluded that it was important for the panel to be convinced of device safety regarding death and myocardial infarction because the study numbers are so small.

Other panel questions concerned the distribution of types of TLR, the total duration of the procedure, the change in definitions and study design during the protocol, the proposed postmarket surveillance program, and the lack of animal studies. Some concerns were expressed over the efficacy data and the need for further studies. Issues involving labeling, dosage range, and the physicians' training program were noted, as was the need for maximizing information presented to consumers as well as physicians.

**OPEN PUBLIC HEARING**

There were no requests to speak.

**OPEN COMMITTEE DISCUSSION (resumed)****FDA Questions to the Panel**

The panel agreed that the definitions for myocardial infarction and target lesion revascularization used in the trial were adequate to assess the clinical performance of the device. In answer to the second question, panel members noted that the company now states it is providing angiographic and clinical follow-up at and beyond nine months. The panel had some debate over the meaningfulness of the definitions of late thrombosis and late total occlusion but agreed that there is no better way known to tease out any difference between the phenomenon without immediate clinical observation. They therefore thought the definitions as adequate as possible to differentiate late stent thrombosis from late total occlusion.

The panel thought the definition used to quantify edge effect was not adequate as given, but actual measurement of the edge effect is possible if required.

The panel agreed that the warning should be revised to include information as it becomes available on late thrombosis. The warning should note that the optimal length of antiplatelet therapy is unknown but an important factor in treatment.

The consensus of the panel was that the probable clinical benefit of the radiation treatment outweighs the probable risks posed by the device in the intended patient population.

On the proposed labeling, the panel suggested that one warning be revised to read: “Do not use in patients who underwent previous intravascular brachytherapy of the same vessel segment or previous radiation treatment in the immediate vicinity of the targeted vessel.” In addition, they suggested a modification to another warning to read: “Do not use in patients with known genetic radiation sensitivity disorders (e.g., ataxia-telangiectasia, etc).”

The panel agreed that a physicians’ training program is critically important and that the device must be used by a multidisciplinary team. Cooperation between the FDA and the NRC on the specifics of regulations that authorize the handling of radiation sources and cooperation through a multidisciplinary approach are likely to continue, as the NRC regulations on prescription of dose calculation and verification are still unfolding. There is an ACGME training program for cardiologists and physicians in handling radioisotopes, which is linked to training and licensing in the ACGME-approved training program in radiation oncology.

The panel agreed that postmarket evaluation should include angiograms and specific evaluation of the irradiated area as well as clinical follow-up of chronic effects of intravascular radiation on the 650 patients of the GAMMA I trial. One long-term routine angiogram three to five years for all 650 patients to look for potential aneurysm formation was suggested. Some members suggested that information on function tests could be provided if available, although there was less panel agreement on this. It was not thought necessary to follow up the placebo

patients, although follow-up on patients to look for repeated incidents as specified in the protocol should be performed.

#### **SPONSOR CLOSING COMMENTS**

There were no requests to address the panel.

#### **FDA CLOSING COMMENTS**

There were no requests to address the panel.

#### **PANEL VOTING INSTRUCTIONS AND OPTIONS**

**Panel Executive Secretary Megan Moynahan** read the voting options and instructions.

A motion was made and seconded to recommend the PMA as approvable with conditions. The conditions were as follows:

- 1) Labeling should be amended as discussed above.
- 2) A multidisciplinary team approach should be required to include physicians and radiation specialists such as an interventional cardiologist, physicist, and oncologist. The sponsor would provide training in a regulated fashion to the team in the hospital setting. This would not just be to meet the criteria for handling of the isotope but also for training in the procedure.
- 3) Postmarketing surveillance would be mandatory, with the FDA standardizing details of the surveillance with the sponsors, but including at a minimum postmarket study of antiplatelet treatment and postapproval data on the premarket cohort for at least five years. Various

specific additional suggestions were made but not necessarily agreed to, including clinical follow-up of the original cohort of GAMMA I patients for long-term adverse events, postmarket surveillance of control patients surveyed in cohort 1 in subsequent trials, and follow-up of both arms of all trials, especially GAMMA I. There was no clear panel agreement on a registry.

The motion to recommend the PMA as approvable subject to the above conditions passed, with a strong recommendation for the FDA to look at experimental models of radiographic long-term patient handling.

FDA representatives thanked the panel members and the audience presenters.

Panel Chairperson Dr. Curtis adjourned the panel for the day at 5:10 p.m.

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**OPEN SESSION—JUNE 20, 2000**

**Panel Chairperson Dr. Anne Curtis** called the Open Session to order at 10:15 a.m.

**Mr. James Dillard, director of the Division of Cardiovascular and Respiratory Devices**, showed an organization chart of the division, noting that it has been reorganized and new personnel added. He noted that three issues were discussed at the last panel meeting, which sought panel input on clinical trial design on rate responsive pacemakers, spinal cord stimulators for treatment of angina, and treatment of atrial fibrillation. He stated that the outcome of that meeting had been helpful both to the FDA and to industry, and he hoped to see more of such meetings in the future. Mr. Dillard presented letters of appreciation and certificates to outgoing panel member Dr. Tony Simmons and outgoing panel chairperson Dr. Anne Curtis.

**Panel Executive Secretary Megan Moynahan** read the conflict of interest statement, noting that waivers had been granted to Drs. Curtis, Hartz, and Vetovec, and that matters concerning Drs. Curtis, Vetovec, Tracy, and Laskey had been considered but deemed unrelated and their full participation would be allowed. Dr. Curtis asked the panel members to introduce themselves.

**OPEN COMMITTEE DISCUSSION—MODIFICATION TO DRAFT GUIDANCE FOR IMPLANTABLE CARDIOVERTER DEFIBRILLATORS**

**Mr. Mike Bazaral of the FDA's Division of Cardiovascular and Respiratory Devices** read the indications for implantable cardioverter defibrillators (ICDs) and the study entry criteria.

He noted an exception for one company, Guidant, which has an additional patient population. Mr. Bazara also read the proposed functional indication for use that does not attempt to specify which patients are at risk of life-threatening ventricular arrhythmias and proposed modifying the guidance document to include that functional indication. Mr. Bazara reviewed four implicit assumptions and read similar functional intended use statements for artificial heart valves and coronary balloon angioplasty devices. He noted that the functional intended use statement for ICDs would be incorporated in the ICD guidance, adding that the proposed indication would replace the current indications in the guidance document and could, at the manufacturer's request, replace the indications for use on currently marketed devices.

#### **OPEN PUBLIC HEARING**

**Hugh Calkins, M.D. of Johns Hopkins University and representing the North American Society for Pacing and Electrophysiology (NASPE)**, discussed the proposed indications for implantable cardioverter defibrillators (ICDs). After a brief review of the function of NASPE, Dr. Calkins stated that NASPE supports the FDA proposed revision to the indications for ICD use. He stated that NASPE agrees with the FDA rationale for the proposed change, which is that current indications for ICD use are out of date vis a vis current clinical practice. He discussed several studies that pertain to the proposed change, such as the AVID trial, AVID registry, and other smaller studies. The rationale for NASPE's support of the proposal, he said, was that NASPE recognizes that the decision to implant an ICD is a medical decision made by

patients and their physicians made on the most current clinical evidence. Professional organizations such as NASPE publish guidelines on the indications for ICD implantation that are updated on a regular basis, and these guidelines also prevent overuse by the medical community.

**Dr. John Fisher of Montefiore and representing Medtronic** discussed the current FDA labeling indications and the proposed changes, as well as the FDA rationale. He listed the potential advantages from a clinician's perspective, which included broader ability to decide on appropriate treatment in an individual case. As a potential clinical disadvantage, he noted the potential for "overuse" of ICDs but said that the medical community has safeguards against such overuse, including professional guidelines. Dr. Fisher stated that as a clinician he supported the proposed change.

**Dr. Marshall Stanton of Medtronic** said that he agrees that the proposed labeling should be adopted. He listed the potential advantages from the industry perspective, which included consistency of indications and promotion of industry cooperation. One potential disadvantage he cited could be discouragement of clinical research on specific high-risk patient populations, but he noted that manufacturers and physicians are committed to supporting clinical research. He concluded that Medtronic strongly supports the proposed change as consistent with current clinical practice, as enhancing timely dissemination of clinical trial data, and as decreasing the regulatory burden.

**Dale DeVries of Guidant**, a company involved in pioneering the technology, stated that Guidant supports the proposed FDA change. He noted that patients have the most to gain by the change in that physicians would then have the flexibility to treat patients at high risk. He agreed with representatives from Medtronic that the proposed change may actually facilitate trials.

#### **OPEN COMMITTEE DISCUSSION**

Panel members asked why the matter was brought to panel, given that the FDA and major manufacturers all agree on the proposed change.

**Mr. Dillard** stated that he heard the very strong consensus of the panel in support of the FDA's making the proposed change. He clarified that while there will no longer be a need for a PMA supplement for a population substudy, there would be a need for some interaction with a sponsor prior to a new indication, and there might still be a need for PMA supplements in the future.

**Dr. Stanton of Medtronic** asked Mr. Dillard to clarify whether a PMA supplement would be needed as long as the promotional data were not related to a specific claim. Mr. Dillard replied that it would still be necessary to check with the FDA; the change means that a supplement is no longer mandatory but still must be discussed with the FDA.

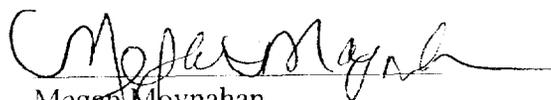
**Dr. Hartz** suggested adding the word "documented" to the last line of the proposed intended use statement to read "treatment of a documented life-threatening ventricular

arrhythmia,” but the rest of the panel disagreed because of the difficulty involved in such documentation.

**Mr. DeVries of Guidant** clarified that a manufacturer can still submit a specific feature for an indication or for a specific patient population, and Mr. Dillard agreed that manufacturers can do so, but it is no longer a necessity.

After reiterating the panel’s support for the proposed change, Panel Chairperson Dr. Curtis adjourned the session at 11:15 a.m.

I certify that I attended the Open Session of the Circulatory Systems Devices Panel Meeting on June 19-20, 2000, and that this summary accurately reflects what transpired.



Megan Moynahan.  
Executive Secretary

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



Anne B. Curtis, M.D.  
Chairperson

Executive Summary prepared by

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