SUMMARY MINUTES

MEETING OF THE CIRCULATORY SYSTEM DEVICES ADVISORY PANEL

OPEN SESSION

November 20, 2003

Gaithersburg Hilton
Gaithersburg, MD

Circulatory System Devices Advisory Panel Meeting
November 20, 2003

Attendees

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

Executive Secretary
Geretta Wood
Food and Drug Administration

Voting Members
Salim Aziz, M.D.
University of Colorado

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

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

Christopher J. White, M.D.
Ochsner Clinic

Consultants
John W. Hirshfeld, M.D.
University of Pennsylvania Medical Center

Douglass A. Morrison, M.D.
University of Arizona

John C. Somberg, M.D.
Rush University

Judah Z. Weinberger, M.D., Ph.D.
Columbia University

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

Industry Representative
Michael Morton
Sorin-COBE CV, Inc.

Consumer Representative
Allen Hughes, Ph.D.
George Mason University

Food and Drug Administration
Bram Zuckerman
Director
Division of Cardiovascular Devices

Jennifer Goode
Biomedical Engineer
Division of Cardiovascular Devices

Stephen Hilbert, M.D., Ph.D.
Experimental Pathologist
Cardiac Support and Prosthetic Devices Branch

John Stuhlmuller, M.D.
Clinician
Interventional Cardiology Devices Branch

Heng Li, Ph.D.
Statistician
Division of Biostatistics

CALL TO ORDER

Panel Chair Warren Laskey, M.D., called the meeting to order at 9:02 a.m. He welcomed the participants and stated that the purpose of the meeting was to discuss and make recommendations on PMA P030025 for Boston Scientific Corporation's TAXUS Express^2 Paclitaxel-Eluting Coronary Stent Systems.

Panel Executive Secretary Geretta Wood read the conflict of interest statement. Waivers had been granted for William Maisel, M.D., M.P.H., and Judah Z. Weinberger, M.D., Ph.D., for their interests in firms that could be affected by the recommendations of the panel. The agency took into consideration matters concerning Drs. Hirshfeld, Morrison, Weinberger, and Yancy, who reported past or current interests involving firms at issue but in matters not related to the day's agenda. Dr. Laskey then asked the panel members to introduce themselves.

Ms. Wood read the appointment to temporary voting status. Panel consultants Hirshfeld, Morrison, Somberg, Weinberger, and Yancy had been appointed as voting members for the duration of the meeting.

Dr. Laskey read a statement from the FDA Commissioner about the agency's desire for transparency in the advisory committee process. Speakers are encouraged to advise the committee of any financial relationship with the sponsor or its competitors, including payment of expenses to attend the meeting.

OPEN PUBLIC HEARING

Kevin McKim, M.A.Sc., Angiometrx Inc., presented information on the Metricath System, a device for sizing stents. A significant number of stents may not appose when only angiography is used for assignment, and angiography alone does not indicate complete stent expansion and

apposition. Sizing is critical in using drug-eluting stents. The Metricath System is a catheter-based technology consisting of a low-pressure balloon that conforms to the size and shape of the artery or stent after it has been deployed; the device enables easy assessment of the cross-sectional area and average diameter. The device is accurate; simple, cost-effective, and safe. Correct stent sizing produces better clinical outcomes and lower risk of complications.

SPONSOR PRESENTATION

Dennis Ocwieja, senior vice president, regulatory affairs and quality, Boston Scientific Corporation, introduced the sponsor speakers and consultants and reviewed the sponsor's agenda. Restenosis is a major limitation of the 800,000 coronary stenting procedures performed each year. Twenty to 30 percent of patients receiving a bare metal stent develop angiographic restenosis, and half require repeat intervention, either percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG). The TAXUS drug-eluting stent was developed to reduce restenosis and the need for repeat intervention. Mr. Ocwieja reviewed the proposed indication for the TAXUS stent and noted that the sponsor's recommendations for the labeling include maintaining patients on a 6-month regimen of aspirin and clopidogrel. A variety of stent lengths and diameters are included in the PMA; the shorter stent lengths are intended to be used in multiple stent procedures to optimize angiographic outcomes.

Mary E. Russell, M.D., medical director and vice president, CV clinical sciences, Boston Scientific Corporation, provided an overview of TAXUS technology. The device has three components: paclitaxel (Taxol), a polymer (Translute), and the stent itself, which is coated with the polymer. The stent provides a dose of paclitaxel equal to 1 $\mu g/mm^2$ stent surface area. After describing paclitaxel's mechanism of action, Dr. Russell noted that antineoplastic use of

paclitaxel requires a high, systemic dose of the drug, whereas antirestenotic use involves a 1400-fold lower dose.

The Translute polymer provides uniform stent coverage, is elastomeric, and provides controlled release of paclitaxel. The polymer is vascular compatible, biostable, and durable in vitro and in vivo. Stability testing demonstrated long-term integrity of the polymer coating. The TAXUS stent releases low concentrations of paclitaxel over a short period of time. The early burst phase is followed by a sustained, slow-release phase of up to 10 days. In the plateau phase, drug is sequestered in the polymer matrix without pathways to the external environment.

Both a slow-release and a moderate-release formulation are under investigation. The in vivo release kinetics are different for the two formulations. Preclinical studies used the moderate-release stent, and the clinical studies used the slow-release stent. Animal studies on release kinetics showed that both formulations plateau at 30 days. Even after intentional coating disruption, only a small amount of sequestered drug is released. The retained drug is sequestered and has no measurable release under physiologic conditions.

Safety has consistently been found in studies of both moderate- and slow-release stents. The preclinical safety data are from 12 studies involving 350 swine and 800 stents implanted with moderate-release stents for up to 360 days. Just two mortalities occurred in 127 pigs receiving 340 stents. No TAXUS-related mortality occurred, nor did any myocardial infarction (MI) or stent thrombosis.

Histological studies found that endothelial cell coverage is complete by 28 days. Microthrombi were equivalent in the control and TAXUS groups at all time points; no gross thrombi developed. Neointimal coverage was found on all struts. At 360 days, results for moderate-release stents included mature neointima and vessel stability; no aneurysms were

found, and medial cell loss was replaced by structural fibrous tissue. No incomplete stent apposition occurred. Late histology supports long-term safety. Similar results were found for overlapping stents.

Parastrut amorphous material (PAM) was present in control and TAXUS animals. PAM is not inflammatory and is sequestered within a maturing neointima. It is not associated with luminal thrombus, erosion, or vessel wall necrosis and, over time, resorbs and heals. Paclitaxel burst release does not inhibit later healing. Strut-associated medial changes did not diminish vessel stability, and calcium deposits, which were present in control and TAXUS subjects, were not associated with structural instability.

Dr. Russell noted that FDA had raised concerns over the histological observations. She emphasized that PAM, medial loss, and calcification did not result in a higher risk of stent thrombosis, aneurysms, incomplete apposition, or dissection in long-term assessments in preclinical or clinical studies with and without overlapping stents. No safety-related adverse events occurred, the healing pattern was progressive, and safety was demonstrated for overlapping stents. Given the animal data establishing the safety of the moderate-release stent, safety has been established for the slow-release TAXUS stent.

The clinical development of TAXUS has involved six randomized trials with more than 3,400 patients in 2003. The pivotal study is the TAXUS IV study, which used slow-release stents. The program has expanded to include three randomized studies and two registries. Dr. Russell summarized data from the TAXUS I and II studies. She noted the possibility of potential systemic interactions with drugs commonly used in CAD pharmacotherapy, but no precedent exists for interactions of those drugs with paclitaxel. Because the TAXUS stent results in paclitaxel plasma levels that are below the lower limit of quantitation, it is unlikely that the stent

will affect metabolism and clearance of other drugs (or vice versa). Hypersensitivity reactions (HSRs) are unlikely with TAXUS stents because the formulation does not include the main culprit for paclitaxel-associated HSRs (Cremophor, which solubilizes paclitaxel for IV dosing).

The early TAXUS clinical studies found efficacy, as measured by clinical data, quantitative coronary angiography (QCA), and intravascular ultrasound (IVUS); the patterns persist out to 2 years. The safety profile is acceptable. Use of the stent resulted in improved MACE rates; no measurable systemic paclitaxel levels; and no vessel enlargement, aneurysms, or late dissections, demonstrating structural stability. The TAXUS I and II findings support the TAXUS IV results.

Gregg W. Stone, M.D., FACC, FSCAI, vice chairman and director of cardiovascular research and education, Cardiac Research Foundation, Lenox Hill Heart and Vascular Institute, reviewed the study algorithm for the TAXUS IV trial. The trial consisted of 1,326 patients undergoing elective stenting at 73 U.S. sites. Because 32 mm stents became available late in the trial, enrollment was expanded by 154 patients to include those patients. Enrollment criteria consisted of a single, de novo lesion coverable by one stent; reference vessel diameter had to be > 2.5 and < 3.75 mm, and lesion length was limited to 10 to 28 mm. Patients were stratified by the presence or absence of diabetes and reference vessel diameter. Patients were randomized to either the study or control group prior to dilatation. A total of 662 study patients received the TAXUS stent; 652 control patients received an uncoated Express stent identical in appearance to the TAXUS stent. At 9-month follow up, 638 patients remained in the TAXUS group, and 632 patients remained in the control group, for a total of 97 percent of the patients. The TAXUS and control groups were comparable in baseline clinical features, such as hypertension and prior MI; target vessel distribution, baseline angiographic data, procedural

results, and the breakdown of stent sizes implanted were similar as well. Patient compliance with antiplatelet therapy was comparable in both groups.

The study endpoints were target vessel revascularization (TVR) and target lesion revascularization (TLR), defined as ischemia-driven repeat PCI or CABG of the target vessel (lesion); target vessel failure (TVF), as evidenced by cardiac death, TVR, or MI related to the target vessel; and MACE, including cardiac death, MI, or TVR. Clinical events were adjudicated by a clinical events committee.

TVR was 61 percent lower and TLR was 73 percent lower in the TAXUS group than in the control group. QCA and IVUS analysis found that in-stent and analysis-segment binary restenosis rates were reduced by 7 percent and 70 percent, respectively, in the TAXUS group. The TAXUS group also had lower late lumen loss both in stent and at the stent edges. All QCA and IVUS variables significantly improved in the TAXUS group, and IVUS improvements were consistent with QCA results.

Safety outcomes consisted of MACE, stent thrombosis, incomplete apposition, aneurysms, and non-MACE significant adverse events. Rates of stent thrombosis were similar for the control and TAXUS groups at 9 months; none were reported between 181 and 270 days. Rates of incomplete apposition, aneurysm, and HSRs were similar in both groups, and no correlation of incomplete apposition with MACE or safety events was found.

An analysis of TLR and restenosis in several patient subgroups looked at the impact of vessel size and lesion length on TLR and restenosis, and it examined the effectiveness of the TAXUS stent in patients with and without diabetes and in patients using glycoprotein IIb/IIIa. The subgroup analysis also looked at outcomes for patients with multiple stents. The TAXUS group had better outcomes than the control group in all subgroup analyses.

Finally, Dr. Russell summarized the company's ongoing efforts to track the long-term safety of TAXUS. She described two surveillance programs outside the United States (WISDOM and MILESTONE II) and the U.S. ARRIVE registry. Through November 14, 2003, a total of 47 stent thromboses (out of 75,864 TAXUS units distributed) had been reported. The company is committed to ongoing postapproval surveillance.

Panel Questions

Panel members asked for clarification on the endothelialization rate in patients with TAXUS stents, intimal thickening, deaths in the study, the dose-response curve for paclitaxel, possible use of the moderate-release formulation in humans, the sponsor's plans for long-term follow up, representativeness of the small number of diabetic subjects, accuracy of the denominators used in calculating study results, chemistry of the surface coating and potential release of sequestered drug, lack of data on clinical events, exclusion of patients with left ventricular dysfunction, and rates of minor complications and adverse events. Sponsor representatives provided additional information.

FDA PRESENTATION

Jennifer Goode, biomedical engineer, Division of Cardiovascular Devices, CDRH, introduced the FDA review team and thanked FDA colleagues in the Center for Drug Evaluation and Research for their assistance in reviewing the device. She summarized the regulatory history of the TAXUS stent and noted that the FDA sent a major deficiency letter to the applicant on September 15, 2003. By November 5, the sponsor had responded to all the deficiencies listed in the letter. The agency and sponsor are working together to resolve outstanding nonclinical and manufacturing issues.

The TAXUS stent is a combination product because it comprises two regulated components (a device and a drug). The Express stent component is currently approved for improving coronary luminal diameter in patients with symptomatic ischemic disease associated with stenotic lesions in native coronary arteries (= 18 mm in length) with reference diameters from 3.0 to 5.0 mm. The label for the bare-metal Express stent does not include a claim for reducing restenosis. The Express stent is approved on both of the proposed delivery systems (monorail and over-the-wire); although the proposed delivery systems were not used in the TAXUS IV trial, the differences are minor and are not expected to affect clinical performance. Paclitaxel has not been approved for the treatment of restenosis or for use in coronary arteries.

The PMA is for stents ranging in length from 8 to 32 mm and of diameters from 2.5 to 3.5 mm. The total drug and polymer per stent are a function of the stent length, irrespective of stent diameter. The agency is evaluating the acceptability of expanding approval to stents of 3.75 mm; use of this size was evaluated in the clinical studies, and no safety concerns arose. Although approval has been requested for a wider range of stent lengths than used in the pivotal study, the study allows for adequate assessment of safety and effectiveness because the amounts of drug substance and polymer are the same as or less than that in the stents implanted in the study.

The sponsor conducted pharmacology and in vivo release studies to assess the elution kinetics and toxicity of the TAXUS stent; it also conducted ISO 10993 biocompatibility testing (of the stent and polymer only). Other nonclinical testing examined stent and delivery system integrity, coating integrity, and sterility and package integrity. Because the applicant did not conduct ISO 10993 testing on the finished product with drug substance, chronic in vivo animal testing was used to evaluate the biocompatibility of the finished product.

Two major clinical issues are outstanding. First, some results from the animal studies suggest the possibility of a low-level continued drug effect in the animal model. Second, FDA is working with the sponsor to finalize protocols and quality control specifications for product stability testing prior to assigning an expiration date for the product. The sponsor has indicated that it has set aside adequate commercial product for conducting stability testing. FDA has not yet completed the review of the recent responses to questions regarding the nonclinical testing. However, no data indicate a safety concern regarding mechanical device failure or malfunction.

Stephen L. Hilbert, M.D., Ph.D., Cardiac Support and Prosthetic Devices Branch, CDRH, summarized the experimental design of the nonclinical in vivo studies. More than 400 stents were implanted in more than 200 swine in the various safety studies that are applicable to the PMA, resulting in hundreds of sections being evaluated in the course of the research. The device handling characteristics are satisfactory, and the device-tissue response is satisfactory with regard to neointimal formation, endothelialization, medial remodeling, and inflammatory response. However, several device-related pathology findings involving medial smooth muscle cell loss, calcification, and PAM require further discussion (see panel question 1).

John Stuhlmuller, M.D., Interventional Cardiology Devices Branch, CDRH, highlighted findings from the TAXUS IV study. Randomization was stratified by clinical site, reference vessel diameter, and the presence or absence of medically treated diabetes. The intent of the stratified randomization was to ensure that an adequate number of patients were enrolled in the various cohorts to be able to determine whether any treatment effects would affect the poolability of the data. The subgroup study was not adequately powered to reach specific conclusions regarding safety and effectiveness, or to support specific marketing claims. At the time of randomization, a designation was also made as to whether the patient would complete

angiographic and/or IVUS follow up. Patients adhered to a 6-month postprocedure antiplatelet regimen of aspirin and clopidogrel or ticlopidine. Multiple stents were used for bailout stenting only; 44 patients received more than one stent. When necessary, a 16 mm stent was used for provisional overlapping.

TVR at 9 months was the principal effectiveness outcome measure; MACE, stent thrombosis, and vessel wall structure were the principal safety outcome measures. The TVR rate was 4.7 percent in the TAXUS arm and 12 percent in the control arm at 9 months. The difference in TVR was due to a reduction in the number of target lesion revascularizations in the TAXUS group. Differences in death and MI rates in the control arm are reflected in the secondary endpoint of TVF. MACE and stent thrombosis rates also were lower in the TAXUS arm than in the control arm. The postprocedure incomplete stent apposition rate was 11.6 percent in the TAXUS arm and 6.4 percent in the control arm; at 270 days, the rate was 4 percent in the TAXUS arm and 3 percent in the control arm. The problem resolved in most cases by 270 days. The late acquired incomplete stent apposition rate was 1.1 percent in the TAXUS arm and 2.2 percent in the control arm. Vessel walls remained structurally intact.

Dr. Stuhlmuller then highlighted findings from the TAXUS I, II, and V studies and of the periapproval study. In TAXUS I, clinical benefit was maintained through 2 years, and the vessel wall remained structurally intact at 2 years; likewise, in TAXUS II, both cohorts saw clinical benefit through 1 year, and similar vessel measurements were seen in both groups at 6 months. No safety issues were noted in TAXUS I or II. TAXUS V is ongoing and has provided preliminary evidence of safety for use in a larger range of lesion sizes. The proposed periapproval study will enroll 2000 patients and has a research plan that is satisfactory to FDA.

Heng Li, Ph.D., mathematical statistician, Division of Biostatistics, CDRH,

summarized the main features of the TAXUS IV study design, conduct, and data analysis. Pretreatment variables were well balanced between the two arms of the study, indicating that randomization was successful. The 12 deregistered patients were excluded from the sponsor's analysis, but excluding such patients from an intent-to-treat analysis of the data creates the potential for bias. The number of deregistered patients was small, however, and was balanced between the two arms; consequently, this approach is acceptable to FDA. Protocol deviations were not extensive, and the different approaches to addressing them did not affect the statistical significance of the results. No safety issues were identified in the subgroup analyses reported in the PMA. The prespecified subgroup analyses for the trial were not powered to make any definitive conclusions.

Following the FDA presentation, panel members asked for clarification on the device's effectiveness in larger vessels, the protocol deviations, whether the sponsor could claim that the device was cytostatic (as opposed to cytotoxic) in the labeling, the carcinogenic potential of the stent, and the stent delivery system used during the trial. The sponsor and FDA representatives provided additional information.

OPEN COMMITTEE DISCUSSION

Christopher J. White, M.D., panel reviewer, focused on the product labeling. He noted that the contraindications specify "known allergy to stainless steel" and suggested that "allergy to nickel" might be more precise. The sponsor should be consistent with the language it has used for other stainless steel stents. The recommendations for antiplatelet therapy in the labeling should specify the regimen used in the pivotal trial, and the precautions regarding patients with tortuous vessels should specify the exact amount of tortuosity that is of concern. The patient guide should

indicate that the device is not magnetic and should emphasize the importance of the antiplatelet regimen. The study was generally well done; the only drawback was that much of the IVUS data was uninterpretable. Dr. White asked for clarification concerning the denominator used in certain tables in the sponsor's submission.

Panel members discussed how long patients with TAXUS stents should wait before having an MRI. Language in the labeling indicates that patients should wait 30 days before having an MRI, but if the device is nonferromagnetic, the patient could theoretically have an MRI the next day. If the stent is ferromagnetic, is the sponsor sure that it is sufficiently endothelialized in 30 days to permit MRI? Dr. Russell noted that the language in the labeling is standard for metal stents, and panel members suggested that the sponsor work with FDA to clarify the instructions concerning MRI. They also suggested that the labeling should state clearly that use of more than two stents has not been adequately evaluated.

Panel members raised additional issues concerning the lack of information in the labeling on the maximum diameter to which the stent may be inflated and the potential for stent–stent and drug–drug interactions, including the ability of sirolimus to inhibit drug delivery. The labeling should state that multiple stents should be of the same material to avoid corrosion. Sponsor representatives indicated that they would include information on stent diameter and noted that there is no consistent evidence of drug–drug interactions with paclitaxel. Panel members also asked for additional information on calcification in animals.

Panel members requested clarification on the sponsor's procedures for randomization; the reasons for excluding the 12 disenrolled subjects from analysis; population baseline characteristics; selection of sites participating in the registry; the need for a more robust clinical profile in the data, particularly to assess clinical impact of the device beyond MACE; intimal

smooth muscle cell loss due to the stent and its relation to incomplete apposition; the rationale for choosing a minimal length of 10 mm at the start of trial and why one-third of the patients did not have lesions within the selected range; availability of data on 8 and 12 mm stents; the likelihood that use of shorter stents will result in frequent multiple stent uses; the concordance rate between investigator and clinical events committee evaluation assessments; inhibition of angiogenesis, and sequestration of PAM. Sponsor representatives provided additional information to the panel's satisfaction.

PANEL QUESTIONS

1. Does the combination of 9 month clinical data from the pivotal TAXUS IV (SR formulation) study and the adjunctive data from TAXUS I (SR formulation) and TAXUS II (SR and MR formulations) adequately address the potential concerns raised by the animal studies?

The panel concurred that at 9 month follow up, the data are convincing, but they are not sufficient to establish safety; long-term follow up would provide greater assurance of safety.

2a. Are the clinical studies presented adequate to address concerns about possible adverse effects from interactions with drugs typically administered to the target patient population?

The panel agreed that the clinical studies were adequate to address concerns about possible adverse drug interactions; no evidence points to interactions of paclitaxel with the drugs most likely to be prescribed among the patient population. At least one member of the panel felt that some theoretical issues in this area had not been evaluated.

2b. Please comment on whether the clinical studies adequately address other drug interactions that are likely to be important or of interest. If not, what other information or studies should be provided? Specifically, please consider the potential for the following types of interactions: (i) with anti-neoplastic agents (ii) with chemotherapeutic agents, where a hypersensitivity reaction could be induced

Panel members concurred that although the sponsor provided little information on the topic, that should not preclude availability of the product. Data should be collected through the existing registries. The drug has finite residence time in the vessel wall, so little cause exists for concern over drug interactions, even on a theoretical basis. FDA and the sponsor should work out the labeling language on contraindications with chemotherapy.

3. Do the clinical data submitted from the pivotal TAXUS IV (SR formulation) study, plus the data from the adjunctive TAXUS I (SR formulation), and TAXUS II (SR and MR formulations) studies, provide reasonable assurance of safety?

The panel concurred that the data do provide reasonable assurance of safety at the 270-day time point; the data do not permit conclusions beyond that point.

4. Does the clinical data at 270 days presented on the TAXUS™ stent from the pivotal TAXUS IV study provide reasonable assurance of effectiveness?

The panel concurred that the data provide reasonable assurance of effectiveness.

5a. Does the evidence presented on the TAXUS™ product support the proposed labeling indication?

The panel agreed that the evidence generally supports the proposed indication. Some panel members felt that the labeling should specify "Express stents," not all bare metal stents; other panel members thought that because actual core lab restenosis rates are similar to those in many other trials, one could say that the data are generic for bare metal stents. The panel concurred that the patient population should be specified as patients with documented ischemia.

5b. Please comment on whether the labeling should specify that multiple stents should only be used for bailout purposes (e.g., dissection, insufficient lesion coverage) and whether in these cases the shortest stent available (i.e., 8 mm) should be used.

The panel concurred that the labeling should specify that multiple stents should be used primarily for bailout purposes. Although it is good for doctors to have access to smaller stents, evidence does not support safety and effectiveness for stent lengths not used in the pivotal trial. Members agreed that it is important for doctors to have access to small stents, for a variety of reasons (e.g., sometimes longer stents are hard to deliver). They noted that if shorter stents are not supplied, physicians will use stents that are not compatible with the TAXUS stent.

5c. Please comment on whether the labeling should address the potential combination of the TAXUS™ stent with an additional drug-eluting stent in the same vessel.

The panel concurred that the labeling should address potential interactions with multiple drug-eluting stents.

5d. Please comment on whether the labeled recommendation for post-procedural antiplatelet regimen is appropriate, and whether additional recommendations on procedural anticoagulation regimens are warranted.

The panel concurred that the recommendation was appropriate. Panel members noted that the sponsor agreed to specify that the regimen should include Plavix, not just any anticoagulant.

5e. Please comment on any other aspects of the product labeling, such as contraindications; warnings/ precautions (such as use with brachytherapy, conjunction with other procedures, etc.); and drug pharmacology, pharmacokinetics or specific drug safety information (e.g., use in special populations, warnings, precautions)

The panel agreed that the current contraindications are adequate. The current labeling, which states that the effects of certain potential drug interactions are unknown, is sufficient. Members voiced concerns about interactions with existing sirolimus stents, other drug interactions, brachytherapy, and radiation therapy and noted that clinicians should be aware that the relation between paclitaxel stents and systemic paclitaxel has not been studied.

6. Please discuss long-term adverse effects that may be associated with TAXUS™ stents, and whether the proposed 5-year follow-up on the clinical trial cohorts and the proposed pre/post-marketing study are appropriate to evaluate the chronic effects of the implantation of the TAXUS™ stent. If not, what additional information should be collected? Specifically, discuss how long patients should be followed, and what endpoints and adverse events should be measured.

The panel concurred that 5-year follow up is appropriate and mandatory. Additional information should be collected on types of patients, circumstances of the procedure, how well the protocol is being adhered to, adverse events, hospitalizations, and cardiovascular sequelae. The intent is to look at low-probability outcomes of interest to clinicians.

OPEN PUBLIC HEARING

Jim Gustafson, vice president, research and development, Possis Medical, Inc., addressed panel on the topic of resolving thrombus before use of drug-eluting stents. Thrombus is present more often than appreciated. Stenting in the presence of unresolved thrombus can cause a "cheese-grater" effect, creating many smaller thrombus particles that would embolize downstream. In addition, unresolved thrombus creates an environment conducive to thrombus formation in the future. Those concerns may be minimized by resolving thrombus before stenting using thrombolytics, glycoprotein IIb/IIIa inhibitors, angioplasty or stenting, or thrombectomy. The AngioJet Thrombectomy Catheter System can remove thrombus safely and effectively. The

panel should consider a more explicit statement in drug-eluting stent labeling regarding the need to remove thrombus prior to using such stents to optimize safety and effectiveness.

VOTE

Executive Secretary Wood read the voting options. The panel voted unanimously to recommend approval of the device with the following conditions:

1. The labeling should specify that patients should receive an antiplatelet regimen of aspirin and clopidogrel or ticlopidine for 6 months following receipt of the stent.
2. The labeling should state that the interaction between the TAXUS stent and stents that elute other compounds has not been studied.
3. The labeling should state the maximum permissible inflation diameter for the TAXUS Express stent.
4. The numbers in the tables in the instructions for use that report on primary effectiveness endpoints should be corrected to reflect the appropriate denominators.
5. The labeling should include the comparator term "bare metal Express stent' in the indications.

POLL

When asked to explain the rationale for their votes, many panel members indicated that the sponsor's data provided compelling evidence of safety and efficacy. Several panel members mentioned that it would be helpful to see clinical endpoints in clinical trials involving future iterations of the device. Some panel members expressed concern over mention of the Express stent in the conditions; other bare metal stents may offer benefit for reduced restenosis, and by specifying a particular stent in the conditions, it could create a problem for future generations of similar devices.

ADJOURNMENT
Dr. Laskey thanked the participants and adjourned the meeting at 4:33 p.m.

I certify that I attended this meeting of the Circulatory System Devices Advisory Panel Meeting on November 20, 2003, 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

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