24 Hour Summary
FDA DES Thrombosis Panel
Circulatory System Devices Panel
December 7-8, 2006

INTRODUCTION

FDA has been monitoring the use of drug eluting stents (DES) since they were approved for use in the United States market in 2003 (Cypher® Sirolimus-Eluting Coronary Stent) and 2004 (Taxus™ Express^{2}™ Paclitaxel-Eluting Coronary Stent). Recent presentations at scientific meetings have suggested a small but significant increase in the rates of: (1) death or myocardial infarction (possibly due to stent thrombosis) and (2) non-cardiac mortality in DES-treated patients compared to patients treated with bare metal stents. FDA has also been evaluating the use patterns of clopidogrel, a drug used in combination with aspirin in patients to reduce/prevent stent thrombosis in DES patients. Although the duration of clopidogrel use appeared to be adequate for the selected patient population in the original clinical trials that supported FDA approval, the optimal duration of clopidogrel in more complex patients has not been established. Though much of the current data that have raised questions regarding the safety of DES have been publicly presented at scientific meetings, relatively little has appeared in peer-reviewed publications or has been independently reviewed by FDA. Nevertheless, DES thrombosis concerns have important public health implications that warrant open an open dialogue among the DES manufacturers, investigators, physicians, and the FDA.

FDA convened this public meeting of the Circulatory System Devices Advisory Panel in an effort to fully characterize the risks, timing and incidence of DES thrombosis. The purposes of this meeting were: (1) to provide a forum for the presentation of clinical data relevant to the issue of DES thrombosis (both when DES are used according to their label and in more complex patients beyond their labeled indication) and (2) to address the appropriate duration of clopidogrel use in DES patients.

The meeting was divided into two days: day one was to discuss the use of DES in accordance with the approved labeled indications. Day two was used to discuss the broader use of DES in "real world" clinical use and to discuss the implications of using this product outside of its approved indications. Dual antiplatelet therapy administration was discussed on both days of the meeting.

CALL TO ORDER (Day 1)

Dr. Maisel called the meeting to order at 8:00 a.m. Geretta Wood, Director of the Advisory Committee Program, read the conflict of interest statement into the record. All members and consultants were in compliance. Based on the agenda and all financial interests reported by the Panel members and consultants, conflict of interest waivers were issued in accordance with 18 U.S.C. Section 208 (b)(3) to Drs. Robert Harrington, JoAnne Lindenfeld, Richard Page, George Vetrovec, and Clyde Yancy. The waivers allowed these individuals to participate in the deliberations. Copies of these waivers may be obtained by visiting the Agency's website at www.fda.gov/ohrms/dockets/default.htm

or by submitting a written request to the Agency's Freedom of Information Office, Room 6-30 of the Parklawn Building. In addition, it was noted that Dr. Judah Weinberger no longer holds a financial interest requiring a conflict of interest waiver. A copy of this statement will be included as part of the official transcript.

On-Label Use of DES

FDA took the floor first and gave an in depth overview of the regulatory history of DES and a discussion of the rigorous review process applied to these products. Takahiro Uchida, M.D., Andrew Farb, M.D., Andrea Holton, Ph.D. and Hesha Duggirala, Ph.D represented the FDA. This in-depth presentation included an overview of DES from a pathological and clinical perspective, including data on stent thrombosis in data submitted to FDA, recent meta-analyses of DES trials, new considerations in the definition of stent thrombosis, an overview of the broad clinical use of DES, and a discussion of antiplatelet therapy issues. The FDA presentation also included FDA-Medical Device Adverse Event Reporting data and an overview of the limitations of available study data.

The first open public hearing session began at 9:30 a.m., each speaker was allotted ten minutes to present.

After a brief break the two sponsors of DES approved in the US (Cordis Corporation and Boston Scientific) were given 30 minutes each to present data on the use of DES in accordance with the FDA-approved indications. These two presentations were followed by the second open public hearing session. These presentations were followed by a one hour lunch break.

Following the break the Panel was given the opportunity to address FDA's questions.

- The panel was in general agreement that DES, when used in accordance to their FDA approved labeled indications, are associated with a clinically important numerical excess of late stent thromboses (after 1 year post-implantation) compared to bare metal stents; however, the magnitude of this excess is uncertain and additional data are needed.
- Based on the analyses presented by the two DES manufactures, the panel concluded that DES were not associated with an increased risk of death or myocardial infarction (MI) compared to bare metal stents despite an apparent increase in stent thrombosis rates after 1-year post-DES implantation. This finding may be due to (1) insufficient sample size in currently available studies; or (2) that an increase in death and MI secondary to DES thrombosis might be offset by a reduction in death and MI associated with in-stent restenosis and additional revascularization procedures in DES patients.
- The panel agreed that when compared to BMS, DES are not associated with an increased rate of all-cause mortality. The Panel requested longer-term follow-up and an increased number of patients in future trials.
- The panel was in agreement that the safety concerns discussed applied equally to the currently approved DES.

- The panel reached consensus that the DES safety concerns do not outweigh their benefits compared to BMS when used within the limits of the approved labeling.
- The panel discussed different options to modifying the labeling for the approved DES.
- The panel was in consensus that the DES labeling should reference the ACC/AHA/SCAI PCI Practice Guidelines for duration of antiplatelet therapy following DES implantation.

Real-World Clinical Use of DES:
Dr. Robert Fiorentino from the FDA presented the Agency's views on "Stent Thrombosis: The Implications of Broader DES Use." Dr. Fiorentino defined the topic of "off-label" use and discussed the potential implications of the finding that the majority of DES are implanted in patients or in vessels with characteristics different than those studied to support marketing approval.

This presentation was followed by two presentations from Boston Scientific and Cordis Corporation. Representatives from each company spoke for 20 minutes followed by a 15 minute Q&A session from the Panel.

Dr. Maisel then announced the fourth open public hearing session. There were a total of six speakers in this session, each speaker was given 10 minutes to present. This final open public hearing session ended with a 20 minute Q&A session by the Panel. Chairman Maisel thanked the participants and adjourned for the day at 6:45 p.m.

CALL TO ORDER (Day 2)
Chairman Maisel called the meeting to order at 8:00 a.m. and Director of the Advisory Committee Program Geretta Wood read the conflict of interest statement into the record.

OPEN PUBLIC HEARING
Chairman Dr. Maisel gave a brief recap of the first day and proceeded to announce the first open the public hearing session of the day, reminding the public of their opportunity to submit written comments. This open public hearing session focused on US experience and discussion on the broader use of DES and its implications.

These presentations were followed by a one hour lunch break. Dr. Maisel announced the third open public hearing session for unscheduled speakers. Each unscheduled speaker was allotted 5 minutes to present. Two unscheduled speakers presented.

Following the unscheduled speakers the Panel was given the opportunity to address the second set of FDA questions.

- The Panel recognized that with more complex patients, there is an expected increased risk in adverse events in these subsets. The panel generally agreed that off-label use of DES is associated with an increased risk of stent thrombosis, death and MI when compared to on-label use of DES. The Panel did not find

sufficient data were available to identify subsets of patients as at a particularly increased risk.

- The panel agreed that at least 12 months of dual antiplatelet therapy should be recommended for off-label uses of DES.
- The panel was unanimous that insufficient available data precluded an opinion regarding whether concerns related to off-label use were similar between the currently approved DES.
- The panel was in agreement that the data on off-label use are limited and recommended that the DES labeling state that results from off-label use of DES should not necessarily be expected to be the same as the results from the clinical trials conducted to support marketing approval.
- The panel called for larger and longer premarket clinical trials and longer follow-up for post-approval studies, with specific definitions related to stent thrombosis events, and more attention paid to patient monitoring and patient compliance .with antiplatelet therapy.

Contact: James Paul Swink 240-276-4179