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FDA Advisory Panel Votes to Keep Avandia on the Market; Society Offers Testimony

In a public hearing held on July 30, 2007, a joint panel of the Endocrinologic and Metabolic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee voted 22-1 to recommend to the U.S. Food and Drug Administration (FDA) that the diabetes drug Avandia (rosiglitazone) be kept on the market with the addition of a black box warning for specific subgroups of patients. After a number of presentations by GlaxoSmithKline (GSK) and the FDA on further analysis of the data related to the potential increased risk of heart attack in patients taking Avandia, committee members agreed by a 20-3 margin that the available data do support the conclusion that Avandia increases the risk of cardiac ischemia in type 2 diabetes patients. However, committee members felt that the many problems with the data and the lack of information on the risk associated with other drugs for diabetic patients precluded a justification of withdrawal of Avandia from the market. Several committee members qualified their vote by stating that a black box warning should be included for specific subgroups of patients, including those taking insulin or nitrates, leading to the final recommendation of the inclusion of such a warning.

The majority of the testimony presented throughout the day by the FDA and GSK focused on the findings from the meta-analysis, observational studies, and randomized controlled trials. The meta-analysis performed by the FDA and GSK suffered the same limitations and showed the same results as the meta-analysis performed by Steven Nissen, author of the original article published in the *New England Journal of Medicine*. All showed that there is a 1.3 to 1.4 hazard ratio for increased cardiac effects of rosiglitazone; however, most of the studies analyzed were short in duration and not designed to look specifically at cardiac events. A number of observational trials that were also analyzed and discussed showed no increased cardiac side effects associated with the drug as compared to other regimens. Finally, testimony from the FDA showed that a number of ongoing large, randomized controlled trials, including RECORD, BARI-2D, and ACCORD, will likely not provide definitive findings on the effects of rosiglitazone on the risk of cardiac events due to design limitations. Because of the conflicting and limited nature of these findings, committee members concurred that the available data are not conclusive enough to justify pulling the drug from the market.

In addition to its attendance at the hearing, the Society submitted written testimony to the committee. The testimony, which may be viewed at the link below, outlined the Society's recommendation that no precipitous action should be taken by the FDA in regard to rosiglitazone and discussed a number of worrisome characteristics of the Nissen study. The

Society supports the decision of the FDA advisory committee to keep rosiglitazone on the market and available to patients while including a warning on the drug's label regarding its possible link to heart disease. To view the Society's press release on the FDA decision, click on the link below:

<http://www.endo-society.org/news/press/EndocrineSocietySupportsFDACommitteeRecommendationsAvandia.cfm>

President Shupnik Represents Society at NIH Peer Review Working Group Meeting

Society President Margaret Shupnik, PhD, attended a July 30 meeting of leaders in the scientific community to discuss the process of peer review at the National Institutes of Health (NIH). The NIH is examining its system of peer review in an effort to streamline operations and make the process more effective. As part of this endeavor, the Advisory Committee to the NIH Director (ACD) has formed a Peer Review Working Group (PRWG)—co-chaired by Society member Keith Yamamoto, PhD, and Lawrence Tabak, PhD—to engage the scientific community and make recommendations to the ACD. As an initial step, the PRWG called a consultative meeting with the scientific leadership of professional societies on July 30, with the PRWG co-chairs and NIH Director Elias Zerhouni, MD, in attendance.

President Shupnik represented the Society at the meeting and conveyed some of the overarching concerns and suggestions of members. She stated that in order to ensure fair and expert review, the best scientists must participate in the process. Voluntary participation and commitment to serve on study sections has waned in recent years, and President Shupnik voiced the concept that grant funding should be tied to service on a review panel. This can be achieved either by requiring all grantees to be in a “pool” of reviewers that may be called upon to serve or by providing additional funding to those grantees who volunteer. She also stressed that continuity of review and reviewers throughout the process for resubmitted grants is necessary for those applications to be judged fairly and effectively.

President Shupnik also emphasized the need for NIH to establish a study section with clinical expertise to review applications for clinical research studies, and she stated that harmonization of Institutional Review Boards (IRBs) will be required to ensure fully fair and equitable review of clinical research applications.

Many professional societies attended the meeting, and several novel ideas were introduced. These included pre-submission of executive summaries of grants and the ranking of unfunded grants by “fundability,” or the probability of future funding. Both suggestions were intended to decrease the investment of time and resources that investigators put into grant applications that have no chance of being funded. These approaches might also help to alleviate the time wasted by the review panels in reading grants that have little merit.

Dr. Yamamoto introduced the idea of changing from the current system of three competitive cycles per year to a system that would function more like an editorial board,

with open deadlines. Some members of the audience echoed and expanded on the idea as the meeting continued, and the concept may be discussed in the future.

Dr. Zerhouni presented a summary describing his take-away messages from the meeting. He stated that the scientific community and NIH shared the common goals of identifying the best science and scientists without bias and with the least burden possible on reviewers and the peer review system. He also listed some concerns that he heard from the societies including the need to balance a broad scientific understanding and focused expertise required for in-depth review of grant applications.

The PWRG will synthesize the information gained from the meeting and present it to the full ACD, along with recommendations on how to move forward.

For more information on the July 30 meeting and the peer review process at NIH, visit <https://www.yesevents.com/nih/regclosed.html>. The NIH has issued a Request for Information (RFI, Notice Number: [NOT-OD-07-074](#)) inviting individual feedback from the scientific community. The Society encourages its members to respond to the RFI.

Endocrine Society Leaders Invite Collaboration from Sister Societies

On Thursday, July 26, The Endocrine Society co-hosted the fifth annual Sister Society Forum with the American Thyroid Association (ATA). Endocrine Society President, Peggy Shupnik, PhD, co-chaired the meeting with ATA President David Cooper, MD. The Society's president-elect Robert Carey, MD, and immediate past president Leonard Wartofsky, MD, were also present to represent the Society. In addition, leaders from the following organizations were in attendance:

- American Association of Clinical Endocrinologists
- American Association of Endocrine Surgeons
- American Diabetes Association
- American Society for Bone & Mineral Research
- American Society of Andrology
- American Society of Endocrine Physician Assistants
- Association of Program Directors in Endocrinology, Diabetes & Metabolism
- Endocrine Nurses Society
- Lawson-Wilkins Pediatric Endocrinology Society
- Society for Gynecologic Investigation

The Sister Society Forum was created to provide an opportunity for endocrine-related organizations to meet and discuss issues of mutual concern and to foster collaboration. This year's forum was organized around advocacy and policy issues, trainee and fellow issues, and global and international partnerships. Many sister society organizations raised issues or proposed initiatives that provided opportunity for collaboration, such as the Society's clinical practice guidelines and its white paper on increasing minority involvement in clinical research.

A list of current sister societies can be found on the Society's Web site at: <http://www.endo-society.org/about/other/fellow.cfm>.

House Approves NIH Funding Measure

The U.S. House of Representatives passed the FY 2008 Labor-Health and Human Services (HHS)-Education appropriations bill, which outlines funding allocations for the National Institutes of Health (NIH), on July 19, 2007 by a vote of 276-140. The bill provides NIH with a \$750 million increase (2.6 percent) over FY 2007 levels. However, because the House bill requires that the NIH transfer \$201 million of this increase to the Global Aids Fund, the net NIH funding increase is \$549 million (1.9 percent) for FY 2008. While this appropriation is a significant increase over the \$231 million cut that the President proposed for NIH, it is well below the FY 2008 6.7 percent increase that the scientific community has recommended. Although the bill passed with a veto-proof margin, it remains to be seen how some of the Republicans who voted for the bill will vote when asked to sustain the President's expected veto. 146 votes are necessary to sustain a Presidential veto in the House.

The full Senate has not yet scheduled a vote on its version of the Labor-HHS appropriations measure, but the Senate Labor-HHS appropriations committee recommended a net \$799 million increase for NIH over FY 2007 levels (2.8 percent). If the Senate approves the appropriations bill with these levels, a final increase for NIH will be established in a conference committee between the two chambers.

Updates will be provided in future issues of *Endocrine Insider*.

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