Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the Endocrinologic and Metabolic Drugs Advisory Committee Meeting
March 28 - 29, 2012

Location: FDA White Oak Campus, Building 31, the Great Room (Rm. 1503), White Oak Conference Center, Silver Spring, Maryland.

Topic: The committee discussed the role of cardiovascular assessment in the pre-approval and post-approval settings for drugs and biologics developed for the treatment of obesity.

These summary minutes for the March 28 - 29, 2012 Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee of the Food and Drug Administration were approved on May 7, 2012

I certify that I attended the March 28 - 29, 2012 meeting of the Endocrinologic and Metabolic Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/Signed/
Paul T. Tran, R.Ph
Designated Federal Officer, EMDAC

/Signed/
Abraham Thomas, M.D., M.P.H.
Chairperson, EMDAC

Summary Minutes of the Endocrinologic and Metabolic Drugs Advisory Committee
March 28 - 29, 2012

The following is the final report of the Endocrinologic and Metabolic Drugs Advisory Committee meeting held on March 28 - 29, 2012. A verbatim transcript will be available in approximately six weeks, sent to the Division of Metabolism and Endocrinology Products and posted on the Food and Drug Administration (FDA) website at: http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/default.htm

All external requests for the meeting transcript should be submitted to the CDER Freedom of Information Office.

The Endocrinologic and Metabolic Drugs Advisory Committee of the FDA, Center for Drug Evaluation and Research, met on March 28 - 29, 2012 at the FDA White Oak Campus, Building 31, The Great Room (Rm. 1503), White Oak Conference Center, Silver Spring, Maryland. Prior to the meeting, the members and temporary voting members were provided the background materials from the FDA. The meeting was called to order by Abraham Thomas, M.D., M.P.H. (Chairperson), and the conflict of interest statement was read into the record by Paul Tran, R.Ph. (Designated Federal Officer). There were approximately 175 people in attendance on March 28 and approximately 125 people in attendance on March 29. There were seven Open Public Hearing speakers.

Issue: The committee discussed the role of cardiovascular assessment in the pre-approval and post-approval settings for drugs and biologics developed for the treatment of obesity.

Attendance:
Endocrinologic and Metabolic Drugs Advisory Committee Members Present (Voting):
Erica H. Brittain, Ph.D.; David M. Capuzzi, M.D., Ph.D., Eric I. Felner, M.D., MSCR; Edward W. Gregg, Ph.D.; Ellen W. Seely, M.D.; Ida L. Spruill, Ph.D., R.N. (*Consumer Representative*); Abraham Thomas, M.D., M.P.H., FACP *(Chairperson)*; Lamont G. Weide, M.D., Ph.D., FACE

Endocrinologic and Metabolic Drugs Advisory Committee Members Not Present (Voting):
Vera Bittner, M.D., M.S.P.H.

Acting Industry Representative to the Committee (Non-Voting)
Mads F. Rasmussen, M.D., Ph.D. *(Acting Industry Representative)*

Temporary Members (Voting):
John H. Alexander, M.D., M.H.S.; Richard N. Bergman, Ph.D.; William O. Cooper, M.D., M.P.H.; Allison B. Goldfine, M.D.; Ed J. Hendricks, M.D.; William R. Hiatt, M.D., FACP; Michael D. Jensen, M.D.; Sanjay Kaul, M.D.; Marvin A. Konstam, M.D.; Judith M. Kramer, M.D., M.S.; Lynn McAfee (*Patient Representative*); Michael A. Proschan, Ph.D.; Peter J. Savage, M.D.; David D. Waters, M.D.; Jack A. Yanovski, M.D., Ph.D.

Speaker (Non-Voting)
William C. Knowler, M.D., Dr.PH

Guest Speakers (Non-Voting)
George A. Bray, M.D., MACP; Robert H. Eckel, M.D., Rena R. Wing, Ph.D.

FDA Participants (Non-Voting):
Eric C. Colman,M.D.; Solomon Iyasu, M.D., M.P.H.; Mary H. Parks, M.D.; Curtis J. Rosebraugh, M.D., M.P.H.; Robert J. Temple, M.D.

Designated Federal Officer: Paul T. Tran, R.Ph

Open Public Hearing Speakers:
Patrick M. O'Neil, Ph.D. – The Obesity Society; George Grunberger, M.D., FACP, FACE – American Association of Clinical Endocrinologists (AACE); Morgan Downey, J.D. – The Downey Obesity Report; Sidney Wolfe, M.D. –Public Citizen; Kelly Close – diatribe; Denise Bruner, M.D., FASBP – American Society of Bariatric Physicians; Preston Klassen – Orexigen Therapeutics, Inc.

The agenda proceeded as follows:

Day 1: Wednesday, March 28, 2012	
Call to Order and Introduction of Committee	**Abraham Thomas, M.D., M.P.H., FACP** Chairperson, EMDAC
Conflict of Interest Statement	**Paul T. Tran, R.Ph** Designated Federal Officer, EMDAC
Introduction/Background Overview of Day 1 Agenda	**Eric C. Colman, M.D.** Deputy Director Division of Metabolism and Endocrinology Products (DMEP), Office of Drug Evaluation (ODE) II Office of New Drugs (OND), CDER, FDA
FDA PRESENTATIONS	
FDA 2007 Draft Guidance for Industry: Developing Products for Weight Management	**Julie Golden, M.D.** Medical Officer DMEP, ODE II, OND, CDER, FDA
Drug Utilization Trends of Anti-Obesity Products in the Outpatient Setting Y1991 - Y2011	**Vicky Borders-Hemphill, Pharm.D.** CDR, USPHS Commissioned Corps Division of Epidemiology II (DE-II) Office of Pharmacovigilance and Epidemiology (OPE), Office of Surveillance and Epidemiology (OSE), CDER, FDA

Duration of Use – Anti-Obesity Drugs	**Christian Hampp, B.S. Pharm., Ph.D.** Visiting Associate/Epidemiologist Division of Epidemiology I (DE-I) OPE, OSE, CDER, FDA

Clarifying Questions from Committee

GUEST SPEAKER PRESENTATION

Pathophysiology of Obesity and Cardiovascular Diseases (CVD)	**Robert H. Eckel, M.D.** Professor in Medicine Director, Lipid Clinic University of Colorado

Clarifying Questions from the Committee

BREAK

SPEAKER PRESENTATION

Obesity and Type 2 Diabetes	**William C. Knowler, M.D., Dr.PH** Chief, Diabetes Epidemiology and Clinical Research Section National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) National Institutes of Health (NIH)

GUEST SPEAKER PRESENTATION

Drugs to Treat Obesity: Cardiovascular and Other Risks	**George A. Bray, M.D., MACP, MACP** Boyd Professor Chief, Division of Clinical Obesity & Metabolism Pennington Biomedical Research Center Louisiana State University

Clarifying Questions from the Committee

LUNCH

GUEST SPEAKER PRESENTATION

Look AHEAD (Action for Health in Diabetes) Trial	**Rena R. Wing, Ph.D.** Professor in Psychiatry & Human Behavior Director, Weight Control and Diabetes Research Center Brown Medical School

FDA PRESENTATION

Statistical Considerations in the Design of Cardiovascular Safety Trials to Rule Out a Pre-specified Cardiovascular Risk *Implications in Trials to Treat Obesity*	**Matthew Soukup, Ph.D.** Lead Mathematical Statistician Division of Biometrics VII, Office of Biostatistics Office of Translational Sciences (OTS), CDER, FDA

Clarifying Questions from the Committee

BREAK

FDA PRESENTATIONS

Cardiovascular Outcomes Trials Experience with Rimonabant and Sibutramine	**Eric C. Colman, M.D.**
Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes: Rationale and Key Features of The Guidance For Industry	**Jean-Marc Guettier, M.D.** Diabetes Team Leader (Acting) DMEP, ODE II, OND, CDER, FDA

Clarifying Questions from the Committee

ADJOURNMENT

Day 2: Thursday, March 29, 2012

Call to Order and Introduction of Committee	**Abraham Thomas, M.D., M.P.H., FACP** Chairperson, EMDAC
Conflict of Interest Statement	**Paul T. Tran, R.Ph** Designated Federal Officer, EMDAC
FDA Remarks	**Eric C. Colman, M.D.** Deputy Director, DMEP, ODE II, OND, CDER, FDA

Open Public Hearing

BREAK

Questions to the Committee and Committee Discussion

LUNCH

Questions to the Committee and Committee Discussion

BREAK

Questions to the Committee and Committee Discussion

ADJOURNMENT

Questions to the Advisory Committee:

1. The current draft obesity drug guidance document recommends that at least 3000 patients be randomized to investigational drug therapy and at least 1500 to placebo in one-year phase 3 trials. To date, most of the patients enrolled in the phase 2 and 3 clinical trials for investigational obesity drugs have very low short-term risk for major adverse cardiovascular events (MACE) (e.g., < 0.5% per year).

   Discuss the potential strengths and weaknesses of enriching the phase 2 and 3 clinical trials with overweight and obese individuals at higher risk for CV events (e.g., history of myocardial infarction, stroke, multiple risk factors) and performing a meta-analysis of prospectively adjudicated MACE.

   Committee Discussion: *The committee noted that one strength of enriching the phase 2 and 3 clinical trials with overweight and obese individuals at higher risk for CV events is that it may be a more accurate assessment of the risk versus benefit profile of anti-obesity drugs. The committee agreed that one of the weaknesses associated with enriching the phase 2 and 3 clinical trials is that such a change would likely require a large shift in the type of population studied in order for sponsors to capture the events needed to complete their trials. The risk for CV events is higher in older patients, thus the enriched study population would likely be comprised of a larger number of older individuals studied over a prolonged period of time in order to see event rates with acceptable confidence intervals (CI). However, this may under-represent the potential for CV risks in younger patients who are at a lower risk but still susceptible, and who are the ones that will actually be using anti-obesity drugs. One committee member cautioned that a low event rate in clinical trials does not necessarily mean that there will be a low event rate outside of the trials. Many committee members noted that cost will be an inhibiting factor if such trial enrichments were required, thus potentially limiting innovation if smaller firms can not perform such trials due to lack of resources.*

   The committee agreed that other ways to ensure event rates are captured would be increasing the duration of treatment and improving the retention rate of study participants. The committee encouraged the sponsors to figure out ways to enhance the retention rate, noting that many trials have had drop-out rates in excess of 50%. The committee noted that careful patient selection would be very important in retention of patients throughout the trials as improving the retention rate would yield more robust data with which to analyze the risk of CV events. The committee also called for more diverse study populations, citing the lack of gender and racial diversity in recent trials which enrolled mostly Caucasian and female study participants. Please see the transcript for details of the committee's discussion.

2. For drugs with a signal for potential CV harm, it should be assumed that sponsors will be required to rule out a certain degree of excess CV risk; e.g., through conduct of a dedicated CV outcomes trial (CVOT) prior to market approval.

   Discuss the potential strengths and weaknesses of the following design parameters of a CVOT for an obesity drug:

a. Ruling out a certain degree of excess CV risk with a pre-approval analysis of a fraction of the planned number of total events, followed by ruling out a smaller excess CV risk with the post-approval final analysis. This assumes that the pre-approval analysis will be based largely on data obtained during the first year of patient exposure, a period of fewer drop outs and maximal weight loss.

Committee Discussion: *There was a general consensus from the committee that it is reasonable to rule out a certain degree of excess CV risk with a pre-approval analysis of a fraction of the planned number of total events, followed by ruling out a smaller excess CV risk with the post-approval final analysis (two-tier design). Several committee members suggested allowing flexibility in terms of what the boundaries should be; for example, allowing more tolerance for CV risks with a more efficacious drug during the first phase of the study. However, it was noted that the boundaries should be stricter during the second phase of the trial which must be able to answer the more definitive CV risks question. The committee also expressed a concern that not allowing a two-tier approach could add excessive costs to trials, causing a delay in drug development and getting new drugs on the market. Additionally, it was noted that the two-tier approach would help provide additional information for the analysis of other potential risks (other than cardiovascular), such as sleep apnea and osteoarthritis. Please see the transcript for details of the committee's discussion.*

b. Setting non-inferiority margins for excess CV risk on the basis of risk difference versus relative risk.

Committee Discussion: *The committee agreed that absolute risk is most important for guiding the patients and treating physicians in making treatment decisions. The committee noted that one of the advantages of using absolute risk rather than relative risk is that absolute risk would be more helpful in estimating the sample size for trial design. Furthermore, the committee noted that comparisons across outcomes can not be done using relative risk and that relative risk is more useful if the event rate is lower than expected. The committee also noted that the type of event occurring should be taken into account when deciding to use the absolute risk versus the relative risk. Lastly, the committee agreed that the trial data must be combinable in order to use the meta-analysis method. Please see the transcript for details of the committee's discussion.*

c. Primary endpoint of strict MACE (CV death, nonfatal MI, nonfatal stroke) versus MACE-Plus (e.g., hospitalized unstable angina, emergent coronary revascularization).

Committee Discussion: *There was a general consensus from the committee that strict MACE is better than using MACE-plus as primary endpoints since MACE-plus is more subjective and can add noise or hide information and obscure what the real risks or real benefits could be. It was noted that if MACE-plus were to be used, it may be better to use less subjective endpoints. Some committee members thought that ischemic revascularization should be a subjective endpoint while others did not. However, there was also a concern that its reliability may be undermined by differences in the way ischemic revascularization is diagnosed. The committee noted some advantages to using MACE-plus, such as the ability to capture event rate increases. Some members*

suggested using a two-tier approach using MACE-plus in the first phase of the trial design and development and then expanding to strict MACE for the approval phase of the trial. Please see the transcript for details of the committee's discussion.

d. Primary analysis population that incorporates on-treatment and off-treatment information (total time analysis population) versus a population that incorporates only on-drug information (on-drug analysis population).

Committee Discussion: *The committee agreed that patients have to be taking the drug in order to assess safety signals. The committee also highlighted the importance of continuing to follow patients who have been taken off the drug in order to identify any further events that are related to safety signals. It was noted that the intent-to-treat (ITT) analysis might be most appropriate for assessing efficacy although it may be of little value to safety assessment. However, there was a concern that ITT may overestimate the benefits. From past experience with other trials, those patients who are more compliant with taking drugs tend to perform better than those patients who are not as compliant, regardless of which treatment arm they may be assigned to. Some committee members suggested that both efficacy and outcomes should be done in the same trial rather than in separate trials of different populations, while other members expressed an opinion that separate analyses may be needed, such as ITT to assess efficacy and on-drug only analysis to assess the safety and risks. Please see the transcript for details of the committee's discussion.*

e. Discontinuing from study drug patients who do not achieve a certain degree of weight loss within the first 3 to 6 months of the trial. Those withdrawn from study drug would continue to be followed.

Committee Discussion: *The committee was concerned that patients may potentially be un-blinded to their treatment assignments if they were withdrawn from the trial due to lack of weight loss. Several committee members expressed concerns that it may be unacceptable to keep patients in a study longer than needed and exposing them to potential side effects when the drug does not offer the benefit of weight loss. Some committee members suggested designing trials with an active run-in period (on-drug) but noted that this trial design may pose difficulties with data analysis when patients are randomized after the run-in period. It was also noted that another disadvantage of using an active run-in period is the elimination of patients who do not have weight loss early on in the trial and the inability to capture adverse events. Please see the transcript for details of the committee's discussion.*

3. (VOTE) Do you believe that obesity drugs <u>without</u> a theoretic risk or signal for CV harm should be required to rule out a certain degree of excess CV risk with a CVOT or an appropriately sized meta-analysis of phase 2 and 3 MACE data?

Vote: Yes: 17 No: 6

a. If you voted "No", please explain why

Committee Discussion: *There was a general consensus from the committee members who voted "No" that obesity drugs without a theoretical risk or signal for CV harm should not be required to rule out a certain degree of excess CV risk with a CVOT or an appropriately sized meta-analysis of phase 2 and 3 MACE data since no other drugs being used for other symptomatic indications are subject to this requirement. The committee expressed that such a requirement would be too costly and would be a disincentive for sponsors to develop newer agents to treat obesity. Please see the transcript for details of the committee's discussion.*

b. If you voted "Yes", please discuss how (CVOT or meta-analysis or both) and when such data should be obtained:

   i. Pre-approval
   ii. Pre- and post-approval (two-staged approach with different non-inferiority margins pre- and post-approval)
   iii. Post-approval

Committee Discussion: *The majority of committee members who voted "Yes" agreed that both CVOT and appropriately sized meta-analysis of phase 2 and 3 MACE data should be conducted. Most members indicated that the data should be obtained using a two-staged approach with different non-inferiority margins pre- and post-approval. Many members noted that they recommend the additional trial and analysis because of the poor safety records of other approved obesity drugs, most of which are no longer on the market. Please see the transcript for details of the committee's discussion.*

The meeting was adjourned at approximately 5:00 p.m. on the first day and approximately 4:15 p.m. on the second day.