Summary Minutes of the
Joint Meeting of the Cardiovascular and Renal Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee
May 2, 2011
Location: FDA White Oak Campus, Building 31, the Great Room, White Oak Conference Center (Rm. 1503), 10903 New Hampshire Avenue, Silver Spring, MD 20993

All external requests for the meeting transcripts should be submitted to the CDER, Freedom of Information office.

These summary minutes for the May 2, 2011 Joint Meeting of the Cardiovascular and Renal Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee of the Food and Drug Administration were approved on ____May 11, 2011_____.

I certify that I attended the May 2, 2011 Joint Meeting of the Cardiovascular and Renal Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

_____**/s/**_____
Nicole Vesely, Pharm.D.
Designated Federal Officer, CRDAC

_____**/s/**_____
Milton Packer, M.D.
Acting Committee Chair

The Cardiovascular and Renal Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met on May 2, 2011 at the FDA White Oak Campus, Building 31, the Great Room, White Oak Conference Center (Rm. 1503), 10903 New Hampshire Avenue, Silver Spring, MD 20993-0002. Prior to the meeting, members and invited consultants were screened and cleared for conflict of interest, and provided copies of the background material from the FDA and the sponsors. The meeting was called to order by Milton Packer, M.D. (Acting Cardiovascular and Renal Drugs Committee Chair); the conflict of interest statement was read into the record by Nicole Vesely, Pharm.D. (Designated Federal Officer). There were approximately 100 persons in attendance. There were three (3) speakers for the Open Public Hearing session.

Issue: The committees met to discuss safety considerations of ultrasound contrast agents (materials intended to improve the clarity of ultrasound imaging), particularly related to new information and developments since the prior Advisory Committee meeting on the same topic on June 24, 2008. The discussion included the results of postmarketing safety studies and data from postmarketing surveillance. Specific drugs discussed included: (1) New drug application (NDA) 21-064, perflutren lipid microsphere injectable suspension, Lantheus Medical Imaging, Inc.; (2) NDA 20-899, perflutren protein-type A microspheres injectable suspension, GE Healthcare; and (3) the investigational new drug (IND) application for sulfur hexafluoride microbubble injection, Bracco Diagnostics, Inc. Perflutren lipid microsphere injectable suspension and perflutren protein-type A microspheres injectable suspension are indicated for use in patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border (improve the clarity of imaging of specific areas of the left lower side of the heart).

Attendance:

Cardiovascular and Renal Drugs Advisory Committee Members Present (Voting):
Henry Black, M.D., Allan Coukell, B.Sc., Pharm. (Consumer Representative), Jonathan Halperin, M.D., Judith Hochman, M.D., Sanjay Kaul, M.D., Mori Krantz, M.D., F.A.C.C., James Neaton, Ph.D.

Drug Safety and Risk Management Advisory Committee Members Present (Voting):
Peter Kaboli, M.D., Elaine Morrato, Dr.PH., Allen Vaida, Pharm.D., Sidney M. Wolfe, M.D. (Consumer Representative), T. Mark Woods, Pharm.D.

Special Government Employee Consultants (Temporary Voting Members):
Ralph D'Agostino, Sr., Ph.D., Milton Packer, M.D. (Acting Chair), Bray Patrick-Lake (Patient Representative), Stuart Rich, M.D., Brian Strom, M.D., M.P.H., Senthil Sundaram, M.D., M.P.H., Michael Weber, M.D.

Regular Government Employee Consultants (Temporary Voting Members):
Vasilios Papademetriou, M.D., Michael Proschan, Ph.D., Vandana Sachdev, M.D., James Tatum, M.D.

Cardiovascular and Renal Drugs Advisory Committee Member (Non-Voting):
Jonathan Fox, M.D., Ph.D., F.A.C.C. (Industry Representative)

Guest Speaker (Non-Voting, Presenting Only):
Sanjiv Kaul, M.D.

Cardiovascular and Renal Drugs Advisory Committee Members Not Attending:
Darren McGuire, M.D., M.H.Sc., F.A.C.C.

Drug Safety and Risk Management Advisory Committee Members Not Attending:
Judith Kramer, M.D., M.S.**,** William Cooper, M.D., Sherine Gabriel, M.D., Sonia Hernandez-Diaz, M.D., Dr.PH, David Madigan, Ph.D., Lewis Nelson, M.D**.,** Maria Suarez-Almazor, M.D., Ph.D., Almut Winterstein, Ph.D.

FDA Participants (Non-Voting):
Janelle Charles, Ph.D., Ross Filice, M.D., Shaw T. Chen, M.D., Ph.D., Solomon Iyasu M.D., M.P.H.

Designated Federal Officer:
Nicole Vesely, Pharm.D.

Open Public Hearing Speakers:
Barry Goldberg, M.D., Co-President of the International Contrast Ultrasound Society (ICUS), Representing the American College of Radiology and the American Institute of Ultrasound in Medicine

Paul A. Grayburn, M.D., Medical Director, Cardiology Research at Baylor University Medical Center, Associate Editor, American Journal of Cardiology, Representing the International Contrast Ultrasound Society

Dr. James Thomas, Moore Chair of Cardiovascular Imagining/Cleveland Clinic, President Elect/American Society of Echocardiography, Representing the American Society of Echocardiography

The agenda was as follows:

Call to Order Introduction of Committee	**Milton Packer, M.D.** Acting Chair, CRDAC
Conflict of Interest Statement	**Nicole Vesely, Pharm.D.** Designated Federal Officer, CRDAC
FDA Presentation Regulatory History of Ultrasound Contrast Agents	**Ira Krefting, M.D.** Deputy Director for Safety, Division of Medical Imaging Products, Office of Drug Evaluation IV, CDER
Speaker Presentation Current Cardiological Applications of Contrast Echocardiography	**Sanjiv Kaul, M.D. (Guest Speaker)** Professor of Medicine and Radiology Head, Division of Cardiovascular Medicine Oregon Health & Science University
Industry Presentation	**Lantheus Medical Imaging, Inc.- perflutren lipid microsphere injectable suspension (Definity)**
DEFINITY® Post Marketing Studies Results	**Mark Hibberd, M.D.** Senior Medical Director, Medical Affairs Lantheus Medical Imaging, Inc.
DEFINITY® Pharmacovigilance Safety Data Review	**Dana Washburn, M.D.** Vice President, Clinical Development & Medical Affairs Lantheus Medical Imaging, Inc.
DEFINITY® Risk/Benefit Profile	**Michael Main, M.D.** Cardiologist

	St. Luke's Mid-America Heart Institute Kansas City, MO
Industry Presentation	**GE Healthcare - perflutren protein-type A microspheres injectable suspension (Optison)**
Introduction and Optison Post-Marketing Safety Data	**Paul Sherwin, M.D., Ph.D.** Senior Medical Director Global Clinical Development GE Healthcare
Post-Marketing Clinical Studies of Optison Safety	**Jonathan Goldman, M.D., FACC, FASE** Executive Vice President-ICON Clinical Research San Francisco, California Assistant Clinical Professor of Medicine, UCSF San Francisco, California
Peer-Reviewed Literature on Optison Human Safety	**Steven Feinstein, M.D., FACC, FESC** Professor of Medicine Director-Echocardiography Lab Rush University Medical Center Chicago, Illinois
Impact of Product Labeling on Patient Care	**Steven Feinstein, M.D., FACC, FESC**
Conclusions	**Paul Sherwin, M.D., Ph.D.**
Industry Presentation	**Bracco Diagnostics, Inc - sulfur hexafluoride microbubble injection (SonoVue)**
Safety Profile of SonoVue® (Sulfur Hexafluoride Microbubbles)	**Alberto Spinazzi, M.D.** Senior Vice President, Group Medical and Regulatory Affairs, Bracco Diagnostics, Inc.
Questions to Industry Presenters	
FDA Presentation Retrospective Observational Cohort VII, Studies for Definity and Optison	**Janelle Charles, Ph.D** Mathematical Statistician, Division of Biometrics Office of Biostatistics, CDER
FDA Presentation (cont.) Postmarketing Studies and Surveillance Of Ultrasound Contrast Agents	**Ross Filice, M.D.** Medical Officer, Division of Medical Imaging Products, Office of Drug Evaluation IV, CDER
Questions to FDA Presenters	

Open Public Hearing

Questions to the Committees

Adjourn

Cardiovascular and Renal Drugs Advisory Committee Questions: May 2, 2011

In 2007, FDA approved revisions of the labeling for Definity and Optison to include a boxed warning, contraindications, and other safety information. These changes were prompted by approximately 200 post-marketing reports of serious cardiopulmonary reactions shortly following administration of the products, including seven deaths. Certain animal modeling studies suggested the agents might acutely induce pulmonary hypertension and systemic hypotension. The 2007 labeling changes were made in the context of premarketing database deficiencies, including the lack of pulmonary hemodynamic data in humans, and a premarketing clinical database that had generally excluded patients with unstable cardiopulmonary conditions.

In 2008, the echocardiography community expressed concern that these new contraindications and monitoring requirements would impose undue limitations on the use of ultrasound contrast agents in critically ill patient populations. Additional information also suggested that the nonclinical pulmonary hemodynamic concerns may not translate to humans. As a result, labeling for Definity and Optison was modified to eliminate certain contraindications and to simplify the monitoring advice. A risk assessment program was also developed which required the sponsors of Definity and Optison to perform:

- A study of pulmonary hemodynamics in humans with and without pulmonary hypertension before and after ultrasound contrast administration
- A prospective safety registry of at least 1000 patients in routine clinical practice
- A retrospective observational study in which mortality is compared between critically ill patients who received a contrast echocardiogram and those who received a noncontrast echocardiogram; comparison was performed using propensity score matching techniques

On June 24, 2008, the Division of Medical Imaging Products (DMIP) in the Center for Drug Evaluation and Research (CDER) at FDA presented these safety data and the planned risk assessment programs to an Advisory Committee. The Committee generally agreed with the Agency's assessments and endorsed the risk assessment plans.

The Advisory Committee met to review the design and results of these post-marketing studies, recent postmarketing data for Definity and Optison, and recent clinical trial and postmarketing data for the investigational agent SonoVue. DMIP sought advice on the utility of these studies for assessing the safety of these contrast agents and for predicting the risks in patients with underlying cardiopulmonary conditions. DMIP did not seeking advice on approval of specific agents; therefore, no voting was required.

Questions (all discussion):

1) Discuss the role of observational studies in addressing rare adverse events that are identified by spontaneous postmarketing reporting.

Questions 1 and 3 were discussed together.

Members noted that observational studies are important for assessing safety signals in the post-marketing phase, however, they also noted that the databases from observational studies have important limitations (e.g. lack of precise time of death, potentially unequal matching due to hidden covariates, cause of death) and that the results do not appear to be robust and are difficult to interpret. Members commented on the studies presented and noted that the Sponsors (GE Healthcare and Lantheus Medical Imaging, Inc.) used the same database, however, differences in the time periods studied and in the analytical approaches resulted in discordant results. Members commented on the use of propensity score matching and the lack of confidence in this matching technique to appropriately balance the different groups. Some members felt that these studies could be more informative if redone by an independent third party with analysis of the raw data from the Premier database and with simultaneous comparison of the two agents with the same methodology.

Please see transcript for detailed discussion.

2) To what extent, if any, do the results of the pulmonary hemodynamic studies provide assurance that Definity and Optison do not acutely induce pulmonary hypertension or worsen underlying pulmonary hypertension?

The Committees felt that the numbers of patients studied was small and that the pulmonary hypertension at baseline was not severe, but that these studies provided "reasonable assurance" that Definity and Optison do not cause significant pulmonary hemodynamic changes. The members did not feel these results were conclusive.

3) The Definity and Optison retrospective observational cohort studies were similar in design. However, unlike the Optison study, the Definity study suggested that patients receiving contrast had lower mortality.

   a. Discuss the appropriateness of the study design, including the time periods studied in relation to the time of approval of safety labeling changes discussed above.

   b. Discuss the apparent lack of consistency in the results between the studies. Does this inconsistency raise questions about the robustness and clinical meaningfulness of the study results?

Questions 1 and 3 were discussed together. Please see Question 1 discussion above.

4) Are data presented conclusive and clinically meaningful to necessitate inclusion within labeling?

Overall, the committee felt that the observational study data presented should not be included in the labeling based on the designs of the studies and the limitations of the results. Several members of the committees felt the results of the safety registry and pulmonary hemodynamic studies were robust enough to include in labeling.

Please see transcript for detailed discussion.

5) To what extent does the totality of all new safety information justify modification of the boxed warnings for these products? Options to consider include:

   a. Complete removal

   b. Modification to reflect less concern

   c. Maintain the current boxed warning

Most committee members did not agree on the options for modifying the boxed warnings for these products. Some members questioned why the boxed warnings were included for the products originally and felt that the boxed warnings should be removed or the language requiring specific monitoring softened. Some also were concerned that leaving the boxed warnings as is may lead to less use of the products in cases where they may be beneficial. Others did not feel that the data presented justified removal or softening of the boxed warning. A comment was made that removing the boxed warning would signal a stronger endorsement of the new data than the committee felt comfortable with. Several members also noted that boxed warnings do not always preclude the use of drugs, and that sales data of ultrasound contrast agents in the United States have rebounded even after the prior addition of the boxed warnings.

Please see transcript for detailed discussion.

Meeting adjourned at approximately 4:10 p.m.