Summary Minutes of the
Cardiovascular and Renal Drugs Advisory Committee
June 24, 2008

Location: Hilton Washington DC/Silver Spring, Maryland Ballroom,
8727 Colesville Road, Silver Spring, MD.

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

These summary minutes for the June 24, 2008 Meeting of the Cardiovascular and Renal Drugs Advisory Committee of the Food and Drug Administration were approved on July 21, 2008.

I certify that I attended the June 24, 2008 meeting of the Cardiovascular and Renal Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

_____**/s/**_____ _____**/s/**_____

Elaine Ferguson M.S.,R.Ph. William R. Hiatt M.D.
Designated Federal Official Committee Chair

Meeting of the Cardiovascular and Renal Drugs Advisory Committee
June 24, 2008

The Cardiovascular and Renal Drugs Advisory Committee, Center for Drug Evaluation and Research met on June 24, 2008 at the Hilton Washington DC/Silver Spring, Maryland Ballroom, 8727 Colesville Road, Silver Spring, MD. Prior to the meeting, the members and the invited consultants had been provided the background material from the FDA. This was a non-voting meeting. There were approximately eighty (80) persons in attendance.

Issue: The committee discussed safety considerations in the development of ultrasound contrast agents, based upon the experience with new drug application (NDA) 21-064, perflutren lipid microsphere injectable suspension, Lantheus Medical Imaging, Inc., NDA 20-899, perflutren protein-type A microspheres injectable suspension, GE Healthcare and the Investigational New Drug Application for sulphur hexafluoride microbubble injection, Bracco Diagnostics. 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 borders.

Attendance:

Cardiovascular and Renal Drugs Advisory Committee Members Present (Voting):
William R. Hiatt, M.D. (Chair) , John M. Flack M.D., M.P.H., Frederick J. Kaskel M.D.,Ph.D., A. Michael Lincoff, MD, FACC, James D. Neaton, Ph.D., Emil P. Paganini, M.D., F.A.C.P., F.R.C.P., Lynne L. Warner Stevenson, M.D., John R. Teerlink, M.D., Steven D. Findlay M.P.H.(Consumer Representative).

Special Government Employee Consultants (Voting):
Professor Ruth S. Day, Mark A Fogel, MD, FACC, FAHA, FAAP, Tal Geva M.D., Sean Hennessy, Pharm.D., Ph.D., Ruth G. Ramsey, MD, James L. Tatum, M.D., Paul H, Zanetti M.D. (Patient Representative)

Industry Representative Members Present (Non-Voting):
Jonathan C Fox, MD, PhD, FACC

Guest Speaker (Non-Voting):
Robert Hamlin, DVM, PhD**,** Sanjiv Kaul, MD

FDA Participants (Non-Voting):
Karen Weiss, M.D., Dwaine Rieves, M.D., Ira Krefting, M.D.

Acting Designated Federal Official:
Elaine Ferguson M.S., R.Ph.

Open Public Hearing Speakers: Barry Goldberg, M.D. American College of Radiology (ACR), American Institute of Ultrasound in Medicine (AIUM), Society of Radiologists in Ultrasound (SRU); William A. Zoghbi, M.D., American Society of Echocardiography; Paul A. Grayburn, M.D. (Speaker for group) and colleagues: Michael L. Main, M.D., Steve B. Feinstein, M.D., Jonathan H. Goldman, M.D.

The agenda was as follows:

8:00 a.m.	Call to Order Introduction of Committee	**William Hiatt, M.D** Chair, CRDAC
	Conflict of Interest Statement	**Elaine Ferguson, M.S.,R.Ph.** Designated Federal Official, CRDAC
8:05 a.m.	FDA Opening Remarks	**Dwaine Rieves, M.D.** Director Division of Medical Imaging and Hematology Products, CDER, OND, OODP
8:15 a.m.	Guest Clinical Speaker Overview of Echo Contrast Agents	**Sanjiv Kaul, M.D.** Professor of Medicine and Radiology Oregon Health and Science University
8:45 a.m.	Guest Preclinical Speaker	**Robert Hamlin, D.V.M., Ph.D.** Professor, Department of Veterinary Biosciences The Ohio State University
	Sponsor Presentations Overview of preclinical and clinical development and postmarketing experience	
9:15 a.m.	Bracco Diagnostics	
	Introduction	**Maurizio Denaro, MD** Group Vice President Research and Development Head Ultrasound Task Force Bracco Imaging
	Sponsor Presentations (continued, Bracco Diagnostics)	
	Clinical Experience and Safety Considerations	**Roxy Senior, MBBS, MD, DM, FRCP, FESC, FACC,** Consultant Cardiologist and Director of Cardiac Research, Honorary Professor, Middlesex University London, Department of Cardiovascular Medicine and Institute of Postgraduate Medical School
	Preclinical Data and Implications for Future Development	**Patricia D. Williams, Ph.D.** Chief Operating Officer Summit Drug Development Services, LLC

	Closing Remarks	**Maurizio Denaro, MD**
10:00 a.m.	**Break**	
10:15 a.m.	GE Health Care	
	Overview of Optison CMC and Preclinical Information and Discussion of Animal Models	**Morten Eriksen, M.D., Ph.D.** GE Health Care
	Optison Clinical Safety Overview and Introduction to Clinical Applications	**Steven B. Feinstein, M.D., F.A.C.C.** Professor of Medicine, Director of the Echocardiography Lab; Rush University Medical Center
11:00 a.m.	Lantheus Medical Imaging, Inc.	
	Definity Non-Clinical Summary	**Dr. Simon Robinson** Senior Director, Pre-clinical Discovery Lantheus Medical Imaging
	Definity Clinical and Post-marketing Summary	**Dr. Michael Main** Mid America Heart Institue
11:45 a.m.	Questions to presenters	
12:00	**Lunch**	
1:00 p.m.	Open Public Hearing	
2:00 p.m.	FDA introductions to questions	**Ira Krefting, M.D.** Acting Associate Director for Safety, Division of Medical Imaging and Hematology Products CDER OND OODP
2:10 p.m.	Discussion of questions to committee	
3:30 p.m.	**Break**	
3:45 p.m.	Discussion of questions to committee (continued)	
5:00 p.m.	Adjourn	

Questions to the Committee

1. Please discuss the relevance of hemodynamic alterations in animals to the reports of serious events in patients, particularly the data from studies in pigs. *reactions in pigs suggestive of similar but very uncommon events in adults*

a. To what extent are the animal data useful in estimating risks for patients with serious underlying conditions (such as acute respiratory failure)? For example, are the findings in pigs more applicable to these patients, compared to the findings in less "sensitive" animals?

b. Are the animal hemodynamic data useful to estimating shared human hemodynamic risks among the UCA? For example, if all UCA produce very similar hemodynamic responses in animals, to what extent does this information suggest that UCA will have similar hemodynamic risks in humans?

Although the committee discussed many of the limitations of animal models, the committee suggested that sensitive and appropriate animal models should be used initially to identify signals and mechanism for possible risk which should inform evaluations in humans.

2. Please discuss optimal ways to establish clinical safety and efficacy of investigational UCA.

a. To what extent can a single arm study design in patients with serious co morbidities identify UCA-related adverse events?

b. What are the potential comparator groups for randomized studies of investigational UCA safety?

c. Does the inability to mask (blind) UCA studies support the use of single arm designs? For example, does the "open label" nature of the studies negate the advantages of a randomized comparator group?

In the case of single-arm studies the committee thought that the risk of an event may be driven more by underlying disease than the contrast agent and therefore risk could not be determined by a single arm study, since the drug effect may not be discernable from the underlying condition. The committee questioned why a blinded study could not be done given the various of levels of blinding that are possible. The committee suggested that there was a need for infrequent serious events to be obtained in well designed, post-marketing observational studies. The committee also emphasized the premarket need for prospective randomized studies in high risk populations who are likely to receive the product, once it is marketed. In this situation, it may not be unrealistic to require adequate exposure under placebo-controlled conditions to exclude a certain level of risk of cardiovascular events (upper end of the 95% CI 1.50 for example).

3. Safety risks for one member of a "class" of drugs may represent risks for all members of the drug class, given similarities among the products. What are the important considerations in determining "class" safety risks for UCA, especially for serious but very uncommon risks that are not likely detectable in the premarket clinical studies?

In addition to any other items, comment upon the limitations and/or importance of:

a. Physical or chemical nature of the products (microbubbles)
b. Mechanism of diagnostic action (echogenic contrast)
c. Effects in animals, e.g., similar hemodynamic responses in pigs

The committee acknowledged certain features of each imaging agent as unique (e.g., specific outer shell and gas component) and noted that some features, but not all, are reasonable to define a "class." The specific features were not discussed in detail.