

**Presentation to the Cardiovascular and Renal Drugs Advisory Committee
On Behalf of
The American Society of Echocardiography
June 24, 2008**

As President of the American Society of Echocardiography (ASE), I am delighted to have the opportunity to provide these comments to the Cardiovascular and Renal Drugs Advisory Committee regarding the safety and clinical utility of echocardiography contrast agents. ASE is an organization of approximately 14,000 physicians, cardiac sonographers, and other professionals committed to excellence in cardiovascular ultrasound and its application to patient care. ASE supports this mission through education, advocacy, research, innovation and service to our members and the public. ASE strongly supports the use of ultrasound contrast agents in clinical practice. There are several reasons for this stance. These agents assist physicians in maximizing the accuracy of information obtained from echocardiograms and in optimizing patient care. Several studies have shown the clinical utility of contrast administration in improving the accuracy of echocardiographic studies in technically difficult patients. In addition, the appropriate use of contrast is extremely cost-effective, since the improved accuracy of echocardiographic studies in difficult-to-image patients impacts patient management and decreases downstream utilization of more invasive—and more costly—procedures. The impact of contrast on patient management has been shown recently to be highest in critically ill patients and ranges between 35% and 65%.

ASE also believes that, while these agents are generally safe and well tolerated, it is important for the clinical community to remain vigilant in monitoring and documenting any unexpected reactions. Any pattern of unanticipated reactions should be carefully studied on a prospective basis. However, as we previously relayed to the FDA, we strongly object to the initial boxed warning that was imposed on echocardiography contrast agents in October 2007. Not unexpectedly, the agency's action provoked a justifiable outcry from our members on behalf of their patients. In this regard, it is especially unfortunate that the black box warning affected, in large measure, populations in whom the administration of contrast is especially useful for patient management.

We are aware of the relative scarcity of safety data that served as a backdrop for the FDA's decision to impose the boxed warning, and we very much appreciate the FDA's decision to reverse some of the contraindications in May 2008, after more data on safety were available. However, we strongly believe that further action is necessary. The negative effects of the initial boxed warning on the appropriate utilization of contrast still linger. Unfortunately, the boxed warning has had a significant deterrent effect on the appropriate use of contrast. Several institutions have decided to stop using contrast all together, thus negatively affecting patient outcome. The end result is non-diagnostic echocardiograms followed by more procedures, at greater risk to the patient and cost to the health-care system. We urge the FDA and industry to collect the safety data necessary

to eliminate or further limit the remaining contraindications pertaining to pulmonary disease and shunting, including the lengthy monitoring period in select patients. In assessing the need to retain the current safety precautions, we urge the agency to consider that, in many cases, the administration of contrast poses a substantially lower risk to the patient than the performance of alternative diagnostic testing, such as transesophageal echocardiography, cardiac CT scans, or cardiac catheterization.

We also urge the agency to look not only to the past, but also to the future, in assessing ultrasound contrast agents. Practicing physicians use ultrasound contrast agents for a number of indications beyond those currently approved by the FDA. These include, among others, stress echocardiography (for LV opacification), vascular imaging and myocardial perfusion imaging. The administration of contrast for these and other indications is supported by numerous studies. ASE believes that echocardiography contrast agents have broad applications beyond that currently approved. We encourage the companies that manufacture these agents to seek agency approval for additional applications expeditiously, as supporting data become available.

Moreover, scientists who are affiliated with ASE and others are performing research on additional applications of echocardiography contrast agents that could have a major impact on patient management in the future. These include molecular imaging, gene and drug delivery, and sonothrombolysis, among others. The Society encourages these scientists and any company interested in developing these applications commercially to seek advice from the FDA early in the product development process, to facilitate the transition from the research laboratory into clinical practice.

Finally, the ASE appreciates the opportunity to have an open dialogue with the FDA regarding the safety and clinical utility of ultrasound contrast agents. We appreciate the opportunity to offer these comments, and hope that both, the agency and industry will call upon us as consideration is given to further narrowing the current contraindications for these agents, and as new and exciting applications of these products are explored in the future. We look forward to ongoing discussions, both formal and informal, with the agency, industry stakeholders and others to bring the clinical benefits of ultrasound contrast agents to full fruition in the care of our patients as expeditiously as possible.

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