



October 3, 2011

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane
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CITIZEN PETITION

I. Introduction

On behalf of the International Contrast Ultrasound Society (“ICUS”)¹, we respectfully submit this Citizen Petition under 21 C.F.R. §§ 10.30 and 201.57(c)(1) to request that the Commissioner of Food and Drugs remove the boxed warnings on ultrasound contrast agents in order to bring the product labeling into line with the current body of scientific research, which now clearly demonstrates the safety and clinical benefits of these radiation-free imaging products.

ICUS members are concerned that current boxed warnings may unduly deter the use of an exceedingly safe, reliable, non-invasive and cost-effective diagnostic imaging tool that does not expose patients to ionizing radiation.

Moreover, given the potential life-saving benefits of ultrasound contrast agents and the potential risks associated their non-use, ICUS believes the boxed warnings are inconsistent with the standards of the Food and Drug Administration (“FDA”) for use of boxed warnings and stand in direct opposition to the FDA’s statutory responsibility to protect promote the health of the American public.

ICUS appreciates that *at the time the FDA required the boxed warnings* there may have been insufficient data to support clinicians’ positive experience with ultrasound contrast agents, and that the FDA’s decision to add boxed warnings was, *at that time*, consistent with its regulatory authority and guidance. As advocates for the best interests of patients, ICUS

¹ ICUS is an international, multi-disciplinary, not-for-profit medical society that is exclusively dedicated to advancing the use of contrast enhanced ultrasound diagnostic imaging to improve patient care worldwide. Founded in September 2008, ICUS brings together physicians, scientists, and other ultrasound imaging professionals from over 55 countries. ICUS members represent diverse specialties such as cardiology, radiology, vascular imaging, gastro-intestinal imaging, oncology, OB-GYN, and hepatology.

members support legitimate and appropriate safety warnings that reflect currently available data.

However, as new scientific evidence emerges, the key question remains whether the available body of safety data warrants the most serious level of caution -- the boxed warning, with the linchpin being how the risks associated with ultrasound contrast agents relate to their benefits. Framed in this way pursuant to the FDA's own guidance, the answer is clear: Ultrasound contrast agents are exceedingly safe and do not warrant boxed warnings. Accordingly, ICUS supports the removal of the boxed warning and a significant modification of the warning in order to reflect current scientific data supporting the safety and clinical benefits of ultrasound contrast agents.

II. Background: Ultrasound contrast agents and CEUS imaging

Contrast-enhanced ultrasound (CEUS) is a radiation-free diagnostic imaging tool that uses an ultrasound contrast agent to improve the clarity and reliability of an ultrasound image.² Ultrasound contrast agents are comprised of liquid suspensions of tiny gas microbubbles. They are injected into a patient's arm vein during an ultrasound diagnostic scan³ and are metabolized and expelled from the body within minutes.

CEUS imaging allows physicians and other health care professionals to identify abnormalities that otherwise might go undetected. In fact, studies show that where no contrast agent is used, 10 to 30 percent of echocardiograms may be inaccurate, exposing patients to potential misdiagnosis or missed diagnoses. By salvaging nondiagnostic ultrasound scans, contrast agents often reduce the need for additional redundant downstream tests that would expose patients to additional risk and costs⁴.

CEUS studies provide immediate real-time information, unlike CT or PET imaging. In addition, CEUS is performed without invasive catheterization using portable equipment. Accordingly, CEUS is widely available in a variety of settings - including the ICU and a physician's outpatient clinic - to improve the reliability of an initial diagnosis or to monitor therapy. Moreover, CEUS presents a strong safety profile with a risk of temporally related

² CEUS also has the potential for new, cutting edge therapeutic uses, such as ultrasound-directed, site-specific drug/gene delivery systems.

³ A CEUS study requires a small amount of an ultrasound contrast agent – ½ to 1 cc, the equivalent to 10-20 drops.

⁴ ICUS recognizes that the reduction of health care costs is a significant issue facing the nation's health care policymakers, and notes that CEUS has been shown to reduce overall health care costs in part by reducing the need for redundant downstream diagnostic testing. Mustafa Kurt, MD, et al., Department of Cardiology, The Methodist Hospital – J Am Coll Cardiol, 2009; 53:802-810, expedited online publication 11 February 2009, © 2009 by the American College of Cardiology Foundation.

death that amounts to approximately 1:500,000 to 1:1,000,000 (even assuming *arguendo* that each and every temporally related death was directly caused by the administration of a contrast agent).

The FDA has approved the use of ultrasound contrast agents for certain forms of cardiac imaging and is considering approval of additional applications. Additionally, outside the United States, CEUS is approved and routinely used for a wider variety of clinical applications, including vascular, liver and other organ perfusion imaging. In fact, it is also used in Europe for monitoring therapy for gastro-intestinal disorders; sentinel lymph node imaging and the assessment of breast (only indication approved), prostate, ovarian, testicular and other cancers.

III. Action Requested

ICUS members are greatly concerned about the deleterious effects of the boxed warnings on the American public's health, and believe that the boxed warnings are unsupported by the current body of scientific research demonstrating a superior safety profile and important benefits to patient care. In support of this Petition, ICUS will demonstrate that:

- a) Boxed warnings are indicated in limited circumstances, such as where the risks of a product are not balanced by its potential benefit;
- b) New scientific data consistently show a positive overall relationship between the risks of ultrasound contrast agents and their benefits; and
- c) The continued use of boxed warnings on contrast ultrasound agents has serious implications for the health of the American public.

Accordingly, for all of the reasons discussed more fully below, ICUS requests that the Commissioner remove the boxed warnings on ultrasound contrast agents. ICUS requests that the Commissioner modify the warnings, outside the black box, to reflect a more appropriate level of concern regarding the safety of these products, consistent with current scientific research demonstrating a favorable risk-benefit ratio.

IV. Statement of Grounds

- A. Boxed warnings are appropriate where the risks are so serious in proportion to the potential benefits that it is essential that they be considered in assessing the risks and benefits of using a drug.**

Pursuant to 21 C.F.R. § 201.57(c)(1), "certain contraindications or serious warnings, particularly those that may lead to death or serious injury, may be required by the FDA to be presented in a box." The FDA's own guidance regarding the appropriate use of boxed warnings states that such warnings can be used to "highlight" situations where "there is an adverse

reaction so serious in proportion to the potential benefit from the drug (e.g., a fatal, life-threatening or permanently disabling adverse reaction) that it is essential that it be considered in assessing the risks and benefits of using a drug.”⁵

Boxed warnings are thus intended to send a clear message -- that certain products are associated with the highest level of risk to patients. Within a hospital risk management context, boxed warnings commonly lead to restrictive risk evaluation and mitigation strategies, policies, guidelines and protocols aimed at protecting patients and averting litigation. These, in turn, may have a chilling effect on CEUS use, potentially to the detriment of patient care. Testimony at the May 2, 2011 Joint Meeting of the Cardiovascular and Renal Drugs Advisory Committee and the Drug Safety Risk Management Advisory Committee (the “Joint Advisory Meeting”) confirmed that hospital liability concerns over boxed warnings often inhibit the use of ultrasound contrast agents.⁶

B. The boxed warnings on ultrasound contrast agents grew out of legitimate safety concerns that pre-dated current scientific research.

In 2007, the FDA required new boxed warnings on both ultrasound contrast agents approved for use in the United States -- Definity (sold by Lantheus Medical Imaging) and Optison (sold by GE Healthcare). The FDA decision grew out of safety concerns relating to an apparent temporal link between four reported deaths and the administration of ultrasound contrast agents in patients who were hospitalized for serious underlying cardiac conditions.⁷ Although the causes of these deaths were unclear at the time, they were taken seriously by the FDA and the medical community.

In 2008, the FDA modified its boxed warnings and requested six additional studies to be performed by the two product sponsors. The action was based on additional data that suggested contrast agents could be used cautiously in unstable patients in whom use was contraindicated by the 2007 boxed warnings, and data suggesting that concerns based on earlier pig studies may not be relevant to humans as pig lungs contain more immunological

⁵ Draft Guidance for Industry: Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products - Content and Format, at 9 (*available at*: <http://www.fda.gov/OHRMS/DOCKETS/98fr/05d-0011-gdl0002.pdf>).

⁶ See May 2, 2011, testimony of Dr. Steven Feinstein, Director, Echocardiography Laboratory, Professor of Medicine Rush University Medical Center, p. 192 of the transcript found at <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM256586.pdf>

⁷ A 2007 FDA report was based on the Adverse Event Reporting System database. The FDA also relied on the results of certain non-clinical studies that reported significant pulmonary and systemic hemodynamic changes after the administration of ultrasound contrast agents in the pig model.

reactive cells than do those of humans. The current boxed warnings for Definity and Optison are attached as Exhibit A.

At the May 2, 2011, Joint Advisory Meeting, FDA consultants reviewed the results of the six sponsor studies and of additional new investigator-initiated studies now published in peer-reviewed medical and scientific journals. A binding recommendation was not sought by the FDA or provided by the consultants.

C. Recent data demonstrate the strong safety profile of ultrasound contrast agents and support the removal of the boxed warnings.

The safety of ultrasound contrast agents has been extensively studied since the FDA decision to require boxed warnings on the product labels for both ultrasound contrast agents. In addition to six safety studies undertaken by the product sponsors, numerous independent investigator-initiated scientific studies have now been published in peer-reviewed medical and scientific journals, showing no increased safety signal even among the sickest patients. These studies also now show that ultrasound contrast agents are not associated with increased risk of death, myocardial infarction, or other morbidity⁸ and that they are safe in patients with pulmonary hypertension, acute myocardial infarction and congestive heart failure, in critically ill patients in the intensive care unit, and in patients undergoing stress testing.

By way of example, a recent meta-analysis of these studies showed that the risk of death for contrast echocardiography was 0.34% (726 / 211,162 patients) versus 0.9% in patients undergoing unenhanced echocardiography (45,970 / 5,078,666 patients).⁹ In studying more than 4.3 million patients, it was found that those receiving a contrast agent were actually 24% less likely to die within 24 hours than patients who did not receive a contrast agent during an ultrasound diagnostic examination.¹⁰ Similarly, the American Society of Echocardiography Multi-Center Registry of thirteen sites and more than 66,000 doses showed (a) no deaths, (b) no serious adverse events in hospitalized patients, (c) severe adverse reactions in 8 non-hospitalized patients (0.01%), and (d) anaphylactoid reactions (severe allergic reactions) in 4 patients (0.006%). The authors of the study concluded that the incidence of severe adverse reactions to ultrasound contrast agents is lower than, or similar to, that reported for contrast agents commonly used in other cardiac imaging tests.¹¹ Further, a meta-analysis of eight controlled observational registry studies, with nearly a quarter million patients, concluded: "the cumulative evidence has suggested that the use of contrast agents for echocardiography is safe

⁸ It is important to note that although these studies were not mandated by FDA, they are consistent with the results of FDA-mandated studies.

⁹ Khawaja et al., *Am J Cardiol* 2010; 106:742-7.

¹⁰ Main ML et al. *Am J Cardiol* 2008;102:1742-6.

¹¹ Wei K. et al. *J Am Soc Echocardiogr* 2008;11:1202-1206.

and not associated with a greater incidence of myocardial infarction (heart attack)" or death.¹² In fact, the meta-analysis actually showed lower mortality rates in patients who received ultrasound contrast recipients. According to the senior author, "we did not see any signal that echo contrast was causing any harm."¹³ This meta-analysis was considered "the latest in a number of studies in recent years to suggest no untoward safety hazard from use of echo contrast agents."¹⁴ This data, gathered retrospectively from significant numbers of patients, demonstrate that contrast is actually safer than non-contrast echocardiography with respect to death.

In 2010, the Ontario (Canada) Health Technology Advisory Committee concluded that there is not a statistically higher mortality rate in patients who receive contrast compared to those who do not.¹⁵

Of course, as with any medical procedure or device, ultrasound contrast agents do carry some associated risks. The most serious is the potential for an anaphylactoid reaction. However, studies have shown that the risk of an anaphylactic reaction from an ultrasound contrast agent is comparable to that of non-ultrasound contrast agents — approximately 1 in 10,000 events. In addition, according to the data from the American Society of Echocardiography Multi-Center Registry, the incidence of severe adverse reactions to ultrasound contrast agents is lower than, or similar to, that reported for contrast agents commonly used for other cardiac imaging.¹⁶ Finally, studies have shown that the majority (65 percent) of patients who experienced an adverse event had a history of allergy.¹⁷

Ultrasound contrast agents also have been shown to elicit complement activation related pseudo allergies ("CARPA"). Ultrasound contrast agents, however, are not alone in this designation. Analgesics, NSAIDs, and liposomes — all of which are commonly prescribed, known to the public, and presented *without a boxed warning* — also have been linked to CARPA.¹⁸ In addition, ultrasound contrast agents, like other contrast agents, may cause acute hypersensitivity reactions. While no prior exposure is necessary to trigger these reactions, reactions to ultrasound contrast agents tend to be milder (or absent) upon repeated exposures, whereas reactions to other contrast agents generally become more severe with each exposure.

¹² Khawaja, et al., "Meta-Analysis of Adverse Cardiovascular Events Associated With Echocardiographic Contrast Agents," *Am J Cardiol* 2010; 106: 742-747.

¹³ Heartwire Aug. 13, 2010.

¹⁴ Id.

¹⁵ Medical Advisory Secretariat, "Stress echocardiography with contrast for the diagnosis of coronary artery disease, an evidence-based analysis," Ontario Health Technology Assessment Series (Internet) 2010 June, Vol. 10, No. 10.

¹⁶ Wei K., et al., *J Am Soc Echocardiography* 2008; 11:1202-1206.

¹⁷ Herzog C.A., *JAMA* 2008; 299:2023-2025

¹⁸ Szebeni, *J Toxicology* 2005; 216:106-121.

Moreover, reactions to ultrasound contrast agents may spontaneously resolve themselves, unlike reactions to their non-ultrasound counterparts.¹⁹

D. New data also demonstrate that the clinical benefits of ultrasound contrast agents are squarely in proportion with, or outweigh, any perceived or actual associated risk.

New research also shows the significant benefits of using contrast agents to improve the reliability of ultrasound diagnostic scans.

1. Accurate and reliable diagnoses. CEUS can decrease un-interpretable results and positively impact therapeutic decisions. A 2009 study found that the appropriate use of CEUS improved endocardial visualization, which, in turn, positively affected diagnostic efficiency and resource utilization and improved patient management.²⁰ The results from this 2009 study showed that by using CEUS physicians were able to decrease the number of un-interpretable studies from 11.7 percent to 0.3 percent. In addition, CEUS changed therapeutic decisions by 10.4 percent, with the highest impact observed in the sickest patient base — *i.e.*, those housed in intensive care units.²¹ Similarly, the Ontario (Canada) Health Technology Advisory Committee in 2010 determined that ultrasound contrast agents improve the diagnostic accuracy of stress echocardiograms and is similar in accuracy to SPECT imaging (which exposes patients to radiation).²²

2. No ionizing radiation. CEUS is ultrasound based and does not utilize any ionizing radiation. By comparison, patients are exposed to ionizing radiation when they undergo SPECT, PET, CT, X-ray and angiography. Although these diagnostic tests may be useful when medically indicated, there is increasing recognition of the over-utilization of radiation-based diagnostic imaging, with significant health concerns due to radiation exposure even at low levels. According to an American Heart Association committee²³:

¹⁹ *Id.*

²⁰ Kurt M., et al., *J Am Coll Cardiol* 2009; 53:802-810.

²¹ *Id.*

²² Medical Advisory Secretariat, "Stress echocardiography with contrast for the diagnosis of coronary artery disease, an evidence-based analysis," Ontario Health Technology Assessment Series (Internet) 2010 June, Vol. 10, No. 10.

²³ Scientific Advisory - American Heart Association Committee on Cardiac Imaging of the Council on Clinical Cardiology and Committee on Cardiovascular Imaging and Intervention of the Council on Cardiovascular Radiology and Intervention, Gerber et al, **Circulation Online Feb 2, 2009: DOI10.1161/CIRCULATIONAHA.108.1916502009.**

- “Medical imaging is the largest controllable source of radiation exposure to the US population, and its most important determinant is the ordering healthcare provider”; and
- “Considerations should include options for answering the clinical question at hand by means that do not use ionizing radiation or choosing the type of study that exposes the patient to the lowest amount of radiation.”

3. No organ toxicity In addition, ultrasound contrast agents do not cause organ toxicity. This eliminates the risk of nephrotoxicity or other organ damage that may occur with contrast agents used in MRI and X-ray.

4. No catheterization, anesthetic or sedation required. CEUS does not require catheterization or anesthetic, both of which are utilized in angiography. In addition, CEUS does not require sedation, which may be utilized in some MRI procedures when patients become claustrophobic.

5. Portable, widely available ultrasound equipment. Because ultrasound equipment can often be taken to the patient, CEUS can be used in a variety of clinical settings -- including the bedside of patients in the intensive care unit who cannot be transported to “big box” imaging equipment. Moreover, ultrasound equipment may be used to image a growing number of severely obese patients who often cannot be imaged with other imaging technology.

6. More cost effective than other forms of imaging. Not only does CEUS reduce the need for redundant downstream tests, as mentioned above, it uses less expensive equipment than the “big box” imaging techniques and does not require a dedicated suite. The 2009 study found that CEUS resulted in a savings of \$122 per patient.²⁴ Moreover, contrast enhanced ultrasound is aligned with current trends in reimbursement: it is most often performed in hospital-based practices; it is based on disease codes rather than procedure codes; and it encourages reductions in reimbursement for other, more expensive, types of imaging.

7. Greater potential for screening and prevention. Because CEUS is free from ionizing radiation, widely available, non-invasive, safe, portable and relatively inexpensive, it offers greater potential for screening, prevention, and ongoing monitoring of patient care.

²⁴ Kurt M., et al., *J Am Coll Cardiol* 2009; 53:802-810.

8. Widespread international acceptance. Physicians throughout the world routinely use CEUS to diagnose heart disease, cancers, digestive disorders, vascular disease, and other conditions and clinical abnormalities in organ systems throughout the body. These clinical uses are based on well established procedures, professional practice guidelines, and peer-reviewed scientific studies from academic institutions across the United States, Europe, Asia, Canada and elsewhere.²⁵

E. CEUS is now required for accreditation of all echocardiography laboratories in the United States.

The positive risk-benefit ratio of CEUS was recently been confirmed by the independent Intersocietal Commission for the Accreditation of Echocardiography Laboratories (“ICAEL”), a member of the Intersocietal Accreditation Commission (“IAC”). ICAEL is dedicated to ensuring quality patient care within the medical specialty of echocardiography.²⁶ In keeping with this mission, the ICAEL develops and provides facility accreditation programs for echocardiography testing. A facility’s ICAEL accreditation is contingent on whether it is in substantial compliance with the *ICAEL Standards*, which set forth the “minimal requirements for echocardiography laboratories to provide high quality care.”²⁷ Since December 2010, ICAEL has included contrast enhanced ultrasound in its *Standards*. In doing so, ICAEL has underscored the important role that ultrasound contrast agents play in improving accuracy. ICAEL recommends, and in some cases requires, the use of contrast agents in certain circumstances.

In addition, in an effort to “improve patient care and health outcomes in a cost effective manner”, The American College of Cardiology, the American Heart Association, the American Society of Echocardiography, and other prominent professional societies have published Appropriate Use Criteria for a variety of cardiovascular testing modalities. In 2011, a combined and updated document was published for transthoracic echocardiography, transesophageal echocardiography, and stress echocardiography. The AUC document indicates use of an

²⁵ See, for example, the CEUS standards and guidelines promulgated by various professional societies around the world:
www.health.gov.on.ca/english/providers/program/mas/tech/reviews/pdf/cardiac_contrast_echo_20100528.pdf; www.wfumb.org/about/statements/ucas.pdf; www.efsumb.org/intro/home.asp;
www.wfumb.org/misc/Affiliate_reports_2011.pdf; www.thieme-connect.de/ejournals/kooperation/81/1314339728825.pdf; www.asecho.org/files/AUCEcho.pdf;
www.asecho.org/files/public/ContrastConsensusStatement.pdf;
www.ejehocard.oxfordjournals.org/content/10/2/194.full?sid=654e7322-fd06-4547-b623-04986fb826de;

²⁶ More information about the ICAEL is available at: <http://www.icael.org>.

²⁷ http://www.icael.org/icael/main/what_is_accreditation.htm.

ultrasound contrast agent is appropriate when “ ≥ 2 contiguous myocardial segments are not seen on non-contrast images.”²⁸

Finally, the Joint Commission, which accredits more than 19,000 health care programs in the US, recently encouraged physicians to use radiation-free diagnostic tests, such as ultrasound or MRI, where feasible in order to avoid exposure to ionizing radiation. According to the organization, exposure to radiation has nearly doubled over the past two decades, and physicians may order tests involving radiation “with no knowledge of when the patient was last irradiated or how much radiation the patient received.” While recognizing that diagnostic radiation can be an effective tool and save lives, the organization urged caution: “The higher the dose of radiation delivered at any one time, however, the greater risk for long-term damage. ... The risks associated with the use of ionizing radiation in diagnostic imaging include cancer, burns and other injuries.”²⁹

V. Conclusion: Failure to remove or modify the boxed warnings could have serious implications for the public’s health.

The threshold criteria used by the FDA to determine whether a particular medication should be assigned a box warning clearly no longer apply to CEUS. When assessing the risks and benefits of using CEUS, one does not find an “adverse reaction so serious in proportion to the potential benefit of the drug” that makes the boxed warning “essential.” Quite the opposite, it would seem that ultrasound contrast agents should be encouraged for a number of important reasons, including: (i) they are exceedingly safe; (ii) they improve diagnostic accuracy; (iii) they help reduce exposure to ionizing radiation; and (iv) they reduce overall health care cost. These benefits are consistent with Administration goals of better care, better health, and lower cost.³⁰ However, unfortunately, the boxed warnings deter use of ultrasound contrast agents, especially in critically ill patients who have the most to gain from a more reliable diagnoses and expeditiously administered therapies.

The risk of use of CEUS is at least partly related to the risk of nonuse, including inaccurate diagnoses or inconclusive results leading to additional redundant diagnostic tests. If

²⁸ Douglas PS, Garcia MJ, Haines DE, Lai WW, Manning WJ, Patel AR, Picard MH, Polk DM, Ragosta M, Ward RP, Weiner RB. ACCF/AHA/ASNC/HFSA/HRS/SCAI/SCCM/SCCT/SCMR 2011 appropriate use criteria for echocardiography, *Journal of the American College of Cardiology* (2010), doi:10.1016/j.jacc.2010.11.002.

²⁹ Radiation Risks of Diagnostic Imaging, The Joint Commission Sentinel Event Alert, Issue 47, August 24, 2011.

³⁰ Affordable Care Act Initiative to Lower Costs, Help Doctors and Hospitals Coordinate Care, Department of Health and Human Services News Release, August 23, 2011, found at: <http://www.hhs.gov/news/press/2011pres/08/20110823a.html>



the boxed warnings remain in place the result for the public, however, will be anything but inconclusive — it will be suboptimal, potentially riskier and more expensive care.

VI. Environmental Impact

Pursuant to 40 C.F.R. § 1508.4 and 21 C.F.R. § 25.30(h), the requested action falls within the categorical exclusion for environmental impact statements.

VII. Economic Impact

Not applicable.

VIII. Certification

Petitioner certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

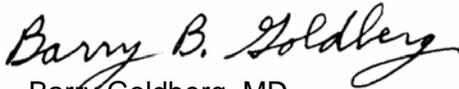
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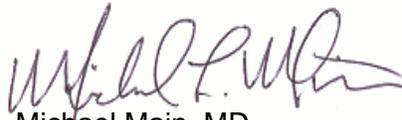
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