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VIA ELECTRONIC SUBMISSION

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Commissioner of Food and Drugs
c/o Dockets Management Staff
Food and Drug Administration
Department of Health and Human
Services
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

CITIZEN PETITION

Request for removal of boxed warnings from labels of
microbubble ultrasound contrast agents (“UCAs”) ¹

Introduction

The undersigned, on behalf of the International Contrast Ultrasound Society 2.0 (“ICUS” or “Petitioner”), respectfully submit this Petition to the Commissioner of the U.S. Food and Drug Administration (“FDA”) under 21 CFR § 10.30, promulgated under the Federal Food, Drug & Cosmetic Act (the “FDC Act”) for the purpose of requesting removal of boxed warnings from UCA product labels and movement of appropriate warnings to the WARNINGS and PRECAUTIONS section of each label.²

¹ UCAs are also sometimes referred to as ultrasound enhancement agents (“UEAs”).

² Petitioner has submitted a separate Citizen Petition to support streamlined consideration and approval of a whole-body indication for UCAs. Additionally, Petitioner submitted a written statement to the FDA in response to the agency’s May 12, 2026 request for information on repurposing approved drugs, and presented comments at the August 5, 2026 Reagan-Udall Foundation for the FDA meeting on repurposing approved drugs, in both cases supporting the repurposing of approved UCAs for broader uses. These efforts recognize that UCAs are systemic agents and their safety and benefits are not organ-specific.

ICUS is a grassroots not-for-profit medical society dedicated to advancing the safe and effective use of contrast enhanced ultrasound (“CEUS”) imaging to improve diagnostic accuracy, disease management and patient outcomes. ICUS members include healthcare professionals, scientists and patients.

CEUS is a safe, affordable imaging modality that uses intravenously-administered UCAs to enhance diagnostic ultrasound images. The use of UCAs has been associated with improved diagnostic accuracy, lower rates of downstream testing and procedures, lower costs, timely detection of disease and delivery of appropriate treatment, and, in some cases, reduced mortality [1-26].

Boxed warnings were added to UCA product labels in 2007. After several modifications, the boxed warnings now caution prescribers that “serious cardiopulmonary reactions, including fatalities,” have occurred uncommonly during or following administration of the UCA³.

Current UCA safety data show that the risk of serious cardiopulmonary reactions is not as serious as previously understood and that the boxed warning is out of proportion with actual UCA safety and benefits [9, 27, 28]. In fact, the data show that UCAs are among the safest forms of contrast media available – and are safer than iodinated contrast agents⁴ and gadolinium agents, which do not have boxed warnings [6, 7, 12, 22, 29-46]. In addition, multi-societal consensus statements now address safe practices across laboratories so that rare risks may be mitigated [8].

The continued presence of boxed warnings on UCA labels fundamentally distorts vital information on which health care decisions are made. When different regulatory standards are applied to UCAs vs. other imaging agents that do not have boxed warnings, despite greater adverse events, the result is misleading information regarding the relative risks and benefits of these imaging options. Ultimately, the “black box” deters judicious utilization of UCAs in patients likely to derive a benefit and creates an independent risk of harm from non-use [11, 12, 47, 48].

21 U.S.C. § 355(o)(4) of the FDC Act grants the FDA authority to require label changes if the agency becomes aware of new safety information. The FDA also has general authority to assure that labeling is not misleading.

³ See Exhibit A, Exhibit B and Exhibit C for current text inside the boxed warning for each FDA-approved UCA.

⁴ Including low-osmolar iodinated contrast.

A. Actions Requested

ICUS respectfully requests that the FDA:

1. Remove the boxed warning from UCA product labels.
2. Move appropriate warnings to the WARNINGS and PRECAUTIONS section of each UCA label.

B. Statement of Grounds

This Statement of Grounds will present the factual and legal grounds on which this Petition relies. These grounds reflect an evidence-based assessment of the safety and benefits of UCAs, outlined as follows:

1. Background: What is CEUS?
2. UCA labeling since 2007.
3. Contemporary evidence of a favorable risk-benefit ratio.
 - a. The numerator: Risk is less severe than previously thought.
 - b. The denominator: Benefits are expanding across new applications.
 - Echocardiography.
 - Liver imaging.
 - Newer applications.
 - Benefits for specific patient populations.
 - Benefits for health care systems.
4. Precedent: Removal of boxed warnings when risk is less severe than previously thought.
5. FDA standards: Insufficient basis for mandating boxed warnings for UCAs.
6. Public health concerns: The UCA “black box” deters appropriate use of safe, beneficial, cost-effective technology.
7. Conclusion.

* * * * *

1. Background: What is CEUS?

CEUS is a diagnostic imaging modality that uses UCAs to enhance ultrasound scans and obtain real-time images of tumors and organ blood vessels in adults and children [14, 49, 50]. CEUS helps physicians identify, characterize and stage tumors and other medical abnormalities of the kidney, breast, thyroid, pancreas, spleen, bowel, musculoskeletal system, testicles, uterus, ovaries and other organ systems [51]. In addition, high resolution CEUS images of the cardiovascular system can dramatically improve the detection and management of cardiac pathology and stratify risk of heart attack or stroke [2, 52-57].

UCAs are comprised of liquid suspensions of gas-filled microbubbles that may be injected intravenously during a diagnostic ultrasound scan. UCAs are smaller than red blood cells and flow through the body's microcirculation without obstruction. After circulating systemically for several minutes, UCAs are safely eliminated from the body as the gaseous microbubble core is exhaled through the lungs and the microbubble shell (lipids or proteins) is metabolized by the liver and spleen.

CEUS examinations use relatively low-cost, portable ultrasound systems that are widely available across a variety of clinical settings -- including the patient's bedside, the intensive care unit and outpatient clinics. CEUS does not expose patients or staff to ionizing radiation, which can increase a patient's cumulative lifetime risk of cancer. In addition, UCAs do not contain gadolinium, iodinated dye or radioactive material, they present no known risk of brain deposits, and they are not known to damage the kidney or other organs [58-60].

CEUS often produces diagnostic images that are equivalent to -- and in some cases are superior to -- images obtained with computed tomography (CT) and magnetic resonance imaging (MR) at higher cost using equipment that is less readily available [19, 61-64]. Additionally, CEUS images are obtained in real time, which can help produce a more timely and accurate initial diagnosis [65], speed access to appropriate therapy, avoid unnecessary downstream tests and procedures [1, 24, 25], lower costs [1, 24, 25], reduce the length of hospital stays [1, 24, 25], improve the efficiency of health care delivery, change patient outcomes and potentially save lives [1, 11, 28].

2. UCA labeling since 2007.

The FDA first mandated boxed warnings on UCAs on October 10, 2007⁵ following spontaneous and isolated reports of four deaths and other serious cardiopulmonary reactions that occurred shortly after UCA administration [66]. All four deaths occurred in patients who had serious underlying illnesses and causation was not contemporaneously adjudicated or established.⁶ The four deaths were later reviewed and attributed to the underlying medical conditions [67].⁷

When the boxed warning was announced, its potential impact was concerning to many cardiologists who had been using UCAs for years without complication and who feared that non-use would jeopardize diagnostic accuracy and patient outcomes [67]. In November 2007, 160 cardiologists and radiologists from around the world signed a letter to Dr. Rafael Dwaine Rieves, then Acting Director of the FDA Division of Medical Imaging and Hematology Products, stating that the new boxed warnings did not reflect the established record of safety and efficacy for UCAs or the potential risks associated with alternative diagnostic procedures or inaccurate non-diagnostic ultrasound scans. In December of 2007, at the invitation of Dr. Rieves, the lead authors met with Dr. Rieves and colleagues and reviewed relevant data.

In May of 2008, after reviewing additional safety reports involving larger cohorts of patients, the FDA modified the boxed warnings, having determined that “the benefits that could be obtained through the use of UCAs may outweigh the risk for serious cardiopulmonary reactions, even among patients at particularly high risk for these reactions” [67]. The FDA also eliminated certain contraindications,⁸ narrowed monitoring instructions, asked sponsors to perform six additional studies, and convened an advisory panel meeting on June 24, 2008 to provide further guidance.

Numerous safety studies were subsequently published in peer-reviewed journals and the results were overwhelmingly favorable [67]. No increased safety signal was found, even

⁵ At the time, two UCAs were approved and marketed in the US: Definity and Optison; however, UCAs are generally treated as a class and Lumason, approved in 2014, also carries a boxed warning.

⁶ One death occurred in a patient with coronary disease during an exercise stress test; one death occurred in the setting of an acute myocardial infarction with severe LV dysfunction; and two deaths were due to pulmonary embolism. Of the two pulmonary embolism patients, one had a history of deep vein thrombosis and coronary artery bypass surgery, and one was in the intensive care unit with cardiomyopathy and severe pneumonia requiring mechanical ventilation and vasopressors. Clearly, all four of these patients had serious underlying diseases that could account for their demise, and event reporting did not determine cause and effect. Event reporting also may be subject to selection bias by the reporting physician.

⁷ One reviewer concluded: “Given the clinical scenarios of the 4 cases and the severity of underlying disease in these patients, death would not be unexpected in any of these patients.”

⁸ The contraindications that were removed include worsening or clinically unstable congestive heart failure, acute myocardial infarction or acute coronary syndromes, serious ventricular arrhythmias or high risk of arrhythmias as a result of prolongation of the QT interval, respiratory failure, severe emphysema, and pulmonary emboli or other conditions that cause pulmonary hypertension.

among the sickest patients. In addition, these studies showed that UCAs were not associated with increased risk of death, myocardial infarction or other morbidity, and they were found to be 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. One study involving 4.3 million patients found that those receiving a UCA-enhanced echocardiogram were 24% less likely to die within 24 hours of contrast administration when compared to patients whose echocardiograms were not UCA-enhanced [12]. Similarly, an analysis of 78,383 contrast doses administered across 13 sites retrospectively found: (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%) [35].

These studies, along with the results of the six new sponsor studies, were reviewed by an FDA joint advisory panel on May 2, 2011. Advisory panel members determined that prospective pulmonary hemodynamic studies provided reasonable assurance that no clinically important hemodynamic changes were seen and specific monitoring requirements inside the boxed warning could be lessened [68]. However, they expressed mixed conclusions regarding the “black box.”

In October 2011, ICUS filed its first Citizen Petition (Docket No. FDA-2011-P-0725), requesting that the “black box” be removed from UCA product labels and the remaining warnings be moved to the WARNINGS and PRECAUTIONS section of each UCA label. The Petition cited the newer safety data, beneficial diagnostic capabilities, and evidence of changed management. The Petition expressed concern that failure to use UCAs where appropriate would potentially increase the risk and expense of misdiagnosis, missed diagnosis and alternative testing. It also stated that the boxed warnings may unduly deter clinically appropriate use of an exceedingly safe, reliable, non-invasive and cost-effective diagnostic imaging tool that does not expose patients to ionizing radiation.

The 2011 ICUS Petition was granted in part – i.e., to the extent of approved label modifications⁹ reflecting updates in the safety profile established by the studies cited by ICUS. The modifications (a) eliminated monitoring requirements for patients with pulmonary hypertension or unstable cardiopulmonary conditions, and (b) added a notation that severe reactions to these agents occur uncommonly. Additionally, in the CLINICAL STUDIES section, new text described the updated safety profile of these agents based on certain of the cited studies. However, the Petition’s request to remove the boxed warning was denied [69].

⁹ Specific labeling modifications were announced in October 2011 for Definity and August 2012 for Optison.

In its written response to the Petition, the FDA provided a detailed and thoughtful assessment of the reliability of the studies cited – and, in effect, a roadmap for future FDA assessment of safety. The agency explained that pulmonary hemodynamic and registry studies conducted by the sponsors were “reliable enough” to warrant label modification because they were prospective, they used a standard definition of adverse events, they had robust patient-level data, and recordkeeping allowed for independent verification of the information collected. However, the FDA cited critical weaknesses in other studies. The weaknesses included failure to control for bias, lack of randomization, retrospective, observational trial design, and incomplete or unavailable patient-level data. These weaknesses have been largely addressed by newer UCA studies discussed below.

The following year, in September 2012, ICUS presented a professional society briefing for the FDA’s Center for Drug Evaluation and Research (“CDER”) and Center for Devices and Radiological Health (“CDRH”). ICUS addressed, among other topics, the importance of CEUS in pediatric imaging and in patients with known or suspected cardiac shunts. ICUS subsequently prepared and published two peer-reviewed scientific papers supporting the safety and efficacy of CEUS in both patient populations [9, 27]. The FDA subsequently removed the cardiac shunt contraindication from all UCA labels and has now approved all three commercially available UCAs for certain pediatric indications.

ICUS also presented a professional society briefing for the FDA Division of Medical Imaging Products in May 2017; submitted a second Citizen Petition on September 4, 2018; and submitted an updated Citizen Petition on August 31, 2020 (citing Docket FDA-2018-P-3354). These communications called the agency’s attention to clinical experience and newer scientific evidence of UCA safety and benefits across diverse clinical settings and patient populations, including adults who are critically ill, patients suffering from COVID-19, and children [6, 7, 11, 12, 22, 23, 31, 33, 34, 36-46, 70]. ICUS also cited new national and international professional guidelines recognizing the benefits of UCAs across a broader range of applications [71-73].

Virtually every major ultrasound organization, along with numerous individual CEUS experts, filed statements supporting the second Citizen Petition and urging removal of the boxed warnings. To our knowledge, not a single statement was submitted in opposition to the second Petition or in favor of retaining the “black box.” The following excerpts illustrate the widespread belief among experts that boxed warnings are outdated in light of current evidence of UCA safety and benefits:

From the World Federation For Ultrasound in Medicine and Biology (WFUMB): “We are surprised that ‘black box warnings’ are still mandated for ultrasound contrast agents, despite extensive scientific research and practice demonstrating their safety. We also are very concerned that the continued requirement of a ‘black box’ unduly

frightens clinicians and ultimately impedes patient access to safe and reliable CEUS imaging where medically indicated.” [74]

From the American Institute of Ultrasound in Medicine (AIUM): “It is the AIUM’s considered opinion that the FDA’s prolonged ‘black box’ warning hinders the delivery of optimal diagnostic imaging services to our patients. We fully support the Citizen Petition filed by the International Contrast Ultrasound Society, and urge removal of the ‘black box’ from the labels of ultrasound contrast agents. We believe that more appropriate labeling, without the unwarranted ‘black box,’ will improve patient care, experiences and outcomes.” [75]

From the Society for Pediatric Radiology (SPR): “Based on the growing body of literature validating the excellent safety profile of ultrasound contrast agents in children and adults coupled with the numerous benefits of CEUS, we believe that the boxed warning is not warranted and only discourages the use of CEUS.” [76]

From the Society of Radiologists in Ultrasound (SRU): “While we appreciate the importance of appropriate safety warnings on drug and device product labels, we believe it is time to update the labeling on UCAs and remove the ‘black box.’ Our extensive clinical experience, along with newer peer-reviewed literature, now clearly show that UCAs present an exceedingly favorable ‘risk-benefit’ ratio. The UCA safety profiles are well-established, and their clinical benefits and indications are expanding. Under these circumstances, the ‘black box’ misrepresents the level of risk associated with UCAs and ultimately deters use of safe and effective imaging tools that can improve outcomes and save lives.” [77]

From the Society of Diagnostic Medical Sonography (SDMS): “The SDMS requests that the Commissioner of Food and Drugs remove the boxed warnings from ultrasound contrast agent product labels to bring the labeling in line with the current scientific research, which now clearly demonstrates the favorable safety profile and clinical benefits of these radiation-free diagnostic imaging products.” [78]

From the American Society of Echocardiography (ASE): “Over the last two decades, a large body of scientific data has clearly demonstrated that ultrasound enhancing agents benefit patient care by improving diagnostic accuracy, reducing error and inter-observer variability, and increasing confidence of interpretation.” [79]

The updated Citizen Petition was denied. In its response, the FDA cited deficiencies involving retrospective observational studies cited in the Petition and the FDA’s own review of FAERS data showing serious cardiopulmonary reactions, including deaths,

occurring since 2007; this Petition cites, *inter alia*, newer scientific literature including a 2026 analysis of FAERS data described below. The response also determined that precedents for removal of other boxed warnings were supported by randomized clinical trials and therefore were not relevant to our Petition; however, newer precedent, described below, represents an independent pathway for “black box” removal based on a comprehensive assessment of contemporary scientific literature and public input, without new randomized clinical trials.

3. Contemporary evidence of a favorable risk-benefit ratio.

Today, the boxed warning on UCA labels may be evaluated with the benefit of decades of post-marketing experience and data demonstrating an extremely low rate of serious adverse events. The issue, therefore, is largely one of risk-benefit reassessment. The numerator of the current risk-benefit ratio is established by extensive contemporary safety data and the denominator is established by growing applications and benefits throughout the body – demonstrating that the risk of a rare idiosyncratic adverse event is outweighed by the expanding benefits of these agents.

a. The numerator: Risk is less severe than previously thought.

Since 2007, the body of reliable scientific evidence has grown and now overwhelmingly shows that UCAs have an excellent safety profile, with absolute risk small and declining [31]. The results of safety studies have been consistent across the decades, and demonstrate that any risk of a serious adverse event is exceedingly low -- with rare allergic and anaphylactoid reactions found in approximately 1:10,000 to 1:15,000 patients [29-31]. That risk is markedly lower than the risks associated with similar contrast media that do not have boxed warnings.

UCAs are now widely considered to be safe and beneficial across expanding indications and populations, in some cases with equivalent or greater efficacy than alternative diagnostic imaging modalities [6, 7, 11, 12, 22, 23, 27, 29, 31-46, 80-83]. The safety record is grounded in decades of post-marketing experience, millions of administered doses, pharmacovigilance databases (including but not limited to FAERS), published meta-analyses and other scientific literature, real-world evidence across adult and pediatric populations, and clinical trials supporting label expansion.

Meanwhile, as clinical experience with UCAs has grown, knowledge of Complement Activation-Related Pseudoallergy (CARPA) risk has matured and safe laboratory practices, developed to mitigate risk, are now routinely implemented in centers across the U.S. [8, 31]. The risk of a CARPA reaction, considered rare in the context of UCAs, is also associated with a wide variety of other drugs and agents including nonsteroidal anti-inflammatory drugs and analgesics that are commonly prescribed and are not subject to

a boxed warning [84]. Safe laboratory practices were recently codified in multi-societal consensus statement¹⁰ published by ICUS and endorsed or supported by the American Society of Echocardiography, the Canadian Society of Echocardiography, the Society of Diagnostic Medical Sonography, the Society for Pediatric Radiology, the British Society of Echocardiography, the World Federation of Ultrasound in Medicine and Biology, the Brazilian College of Radiology, the Joint Review Committee for Diagnostic Medical Sonography, the Chinese Ultrasound Doctors Association, the Association for Medical Ultrasound, the American Society of Neuroimaging, and the Society for Vascular Ultrasound [8].

The following examples illustrate some of the findings of key UCA safety studies, virtually all of which were published after 2007:

- i. **A 2026 re-analysis of FAERS data indicated that the overall risk of adverse events remains small in absolute numbers, and UCA risks were lower than risks associated with gadolinium and iodinated contrast agents which do not have boxed warnings.** The study also found that, while absolute numbers of adverse events increased during the COVID-19 pandemic, the increases were commensurate with changes in reporting during this period [31].
- ii. A 2025 study – the largest to date -- examined the safety of UCA use among 500,073 recipients drawn from a nationwide cohort of 11.4 million patients across the US between 2018-2022. Those receiving UCAs were significantly less likely to die or experience serious cardiopulmonary events within 48 hours, regardless of year or brand of agent. Matched analyses accounted for higher use in more medically complex patients and during the COVID-19 pandemic period [11].
- iii. Recent studies have examined the potential for polyethylene glycol (PEG)-associated risk¹¹ and the apparent confounding associated with time period and route of administration [11, 31]. True allergic reaction to PEG is estimated to occur < 1 per million patients [31] and strategies have been developed to screen patients for the presence of allergy if suspected [85].
- iv. Serious adverse events from abdominal contrast scanning are low, at 0.0086% among 23,188 examinations, without any deaths reported. UCAs are not

¹⁰ The consensus statement established clear standards for safe laboratory practices that are consistent with recommendations provided by Radiology bodies for use of gadolinium and iodinated contrast.

¹¹ Lipid-based UCAs, Definity and Lumason, contain PEG. Optison, which has an albumin shell, does not contain PEG.

nephrotoxic and do not collect in the renal spaces; additionally, they do not carry risks associated with iodized contrast agents used in CT or gadolinium contrast agents used in MR [3, 14, 86].

- v. A 2014 study by Main et al. reviewed UCA use in 1,006,381 patients and found a 28% lower mortality rate in critically ill hospitalized patients whose echocardiograms were UCA-enhanced compared to propensity-matched patients whose echocardiograms were unenhanced [45]. The difference between groups was observed at 48 hours and throughout the hospital stay.
- vi. As noted above, Main et al., examined UCA use in 4,300,966 hospitalized patients, as documented in the Premier Perspective Database. Patients receiving a UCA-enhanced echocardiogram were 24% less likely to die within 24 hours of administration when compared to patients whose echocardiograms were unenhanced -- even though the patients receiving UCAs were more likely to have worsening or unstable heart failure, acute coronary syndrome/acute myocardial infarctions, ventricular arrhythmias, and respiratory failure [12].
- vii. A 2017 retrospective study of 30,222 patients at a large hospital in China found no fatalities and adverse events in only six patients (0.02%), two of which were serious (0.007%) [82]. Similarly, a retrospective study of 23,188 UCA administrations across 28 Italian medical centers found no fatalities and only 29 adverse events, two of which were serious (0.0086%) [3].
- viii. Another study found no short term or long-term increased risk of death or heart attack associated with UCAs in patients who underwent stress echocardiography [39].
- ix. Several studies have demonstrated that UCAs appear to be safe in patients with pulmonary hypertension [29, 36, 43].
- x. Pediatric CEUS safety studies demonstrate very few adverse events, including serious adverse events, in children. In addition, pediatric CEUS helps reduce the need for other imaging modalities with greater risk – including some pediatric fluoroscopic exams and CT exams [9]. CT scans are the single largest contributor to medical radiation exposure in the United States; avoidance is particularly important for children because they are more sensitive to ionizing radiation than adults and the cancer risk associated with exposure to ionizing radiation is cumulative over a patient's lifetime [87].
- xi. CEUS also may reduce the need for pediatric MR and MR contrast agents, which present unknown long-term consequences associated with deposition in

various organs, particularly the brain. The FDA now requires a new class warning and other safety measures for all gadolinium-based contrast agents for MR concerning possible links to adverse health effects from gadolinium retention in patients' bodies, including the brain, months to years after receiving these drugs [88]. This is of particular concern in children, whose brains are still developing.

- xii. CEUS is a patient-friendly imaging modality that does not require sedation or anesthesia, which entail their own risk of adverse events [87].
- xiii. UCAs improved image interpretation in 83% of patients with left ventricular assist devices ("LVADs"), who are among the sickest patients, and no adverse events or known side effects were reported during or after the CEUS examinations. In addition, LVAD function was not affected during or after CEUS [80, 89].
- xiv. UCAs reduced the use of redundant downstream diagnostic imaging -- which may expose patients to added, unnecessary risk. In patients with technically difficult echocardiograms, CEUS changed patient management in 35.6% of patients overall, resulted in procedures avoided in 32.8%, and had the greatest impact on the care of the sickest patients, 62.9% of whose management was changed [1].
- xv. In the six safety studies requested by the FDA and designed collaboratively by the agency and UCA manufacturers, no deaths or SAEs occurred and there was no significant change in pulmonary artery systolic pressure or pulmonary vascular resistance after UCA dosing. In addition, there was no increased mortality risk in critically ill patients [29].

Furthermore, the risk of non-use has been demonstrated consistently over nearly two decades [11, 45]. This is important because diagnostic errors contribute to 10% of patient deaths [90, 91]. To the extent that a widely available and safe tool exists to improve diagnostic accuracy and timeliness, but use is deterred by regulatory labeling [32], the FDA now has an important opportunity to reassess the risks and benefits of UCAs and modify labeling in light of current data and the best interests of patients.

b. The denominator: Benefits are expanding across new applications.

The dramatic expansion of new UCA applications since 2007 has fundamentally changed the denominator of the risk-benefit ratio. New studies and professional guidelines support the use of UCAs in adults and children to help detect, characterize and manage treatment of serious and sometimes fatal cancers and other abnormalities of the liver, kidney,

breast, thyroid, pancreas, spleen, bowel, gall bladder, musculoskeletal system, testicles, uterus and ovaries; detect organ injury following acute trauma; stratify and manage risk of cardiovascular events; provide guidance in interventional procedures; and monitor therapy. Potential benefits span outpatient and hospital settings, and are experienced by critically ill patients and those with serious cardiopulmonary conditions [2, 8].

Studies now show that CEUS may be as accurate as CT and MR, and in some cases CEUS is clearly superior to unenhanced CT or MR for detection and diagnosis of pathology. CEUS also provides diagnostic information unavailable from unenhanced CT or MR while offering distinct advantages of dynamic real-time assessment of vascularity and tissue perfusion with excellent sensitivity and the highest spatial resolution of any imaging modality [50, 61-64, 92, 93]. UCAs are considered ideal agents for assessing perfusion of tumors and organ systems because, unlike CT and MR contrast agents, UCAs do not leak into interstitial spaces [58-60, 94]. And, gadolinium-based contrast agents used in MR imaging may leave behind trace amounts of the heavy metal with unknown long-term consequences.

As UCA uses and benefits expand, the new denominator provides a clear and independent basis for concluding that the rare risk of adverse events associated with UCAs is far outweighed by their compelling and often life-saving benefits.

i. Echocardiography.

Initially, UCA benefits were largely limited to adult echocardiography, with approved indications for opacification of the left ventricular chamber of the heart and delineation of the left ventricular endocardial border in patients with suboptimal echocardiograms. Today's echocardiographers use UCAs for a much broader range of uses, including quantification of LV volumes and ejection fraction; regional wall motion assessment; LV thrombus detection; cardiac mass characterization (differentiating avascular thrombi from vascular tumors); evaluation of apical hypertrophic cardiomyopathy, apical aneurysms, LV noncompaction, and pseudoaneurysm; left atrial appendage assessment during transesophageal echo (e.g., thrombus exclusion before cardioversion); stress echocardiography — wall motion and myocardial perfusion for coronary artery disease/ischemia/viability; critical care/ICU imaging of technically difficult patients; evaluation of chest pain with nondiagnostic electrocardiogram; post-STEMI microvascular obstruction assessment; vascular imaging including carotid, femoral, aortic dissection, and endoleak detection; pediatric and congenital heart disease imaging; Doppler signal enhancement (tricuspid regurgitant jets, valvular stenosis velocities); and various emerging applications such as sonothrombolysis, molecular imaging, and targeted delivery of cancer drugs and gene therapies. UCAs also improve reproducibility of left ventricular volumes and ejection fraction comparable to that of the "gold standard"

of cardiac MR [95, 96], improve the interobserver variability of wall motion abnormalities [96] including augmenting the sensitivity and specificity of stress echocardiography [26, 52, 95], improve distinction of vascular and avascular intracardiac masses [97], better identify apical hypertrophic cardiomyopathy and associated aneurysm [71, 98], improve confidence for thrombus exclusion in transesophageal echocardiography prior to cardioversion [99] with at least one small study suggesting a reduction in embolic events [100], and improve detection of coronary artery disease and associated risks [53, 101-103].

Echocardiographers also use UCAs to salvage non-diagnostic echocardiograms and identify cardiac abnormalities that otherwise might go undetected, exposing patients to the risk of misdiagnosis or a missed diagnosis. Some 10-20% of resting echocardiograms, and 33% of stress echocardiograms, may be technically difficult or uninterpretable due to inadequate resolution [71, 73, 103], and non-diagnostic ultrasound scans may be even more prevalent in particular patient populations - e.g., obese patients, patients with breast cancer or lung disease, and patients with LVADs [1, 71, 98, 104, 105]. When UCAs are used to salvage non-diagnostic echocardiograms, patients are often spared the expense, risk and inconvenience of redundant downstream testing [1, 24, 25]. Additionally, quantitative uptake of UCAs may be used as a blood tracer to measure myocardial blood flow, with equivalent specificity but higher sensitivity and prognostic value when compared to standard single-photon emission CT [106-111].

ii. Liver imaging.

Liver indications now represent some of the most compelling examples of expanded UCA benefits since 2007. For example, CEUS is often used to assess hepatocellular carcinoma (HCC) -- the most common form of primary liver cancer, which is the third leading cause of cancer-related death worldwide [112] and continues to rise in incidence among U.S. women [113]. In patients at risk for developing HCC, UCAs are used to characterize nodules detected by routine grayscale ultrasound surveillance. CEUS may also help differentiate between HCC and intrahepatic cholangiocarcinoma (ICC), the second most common malignant liver tumor; this differentiation is critical when treatment options are chosen [94]. CEUS also helps identify and characterize focal liver lesions (FLLs) [114]. The addition of CEUS to liver imaging protocols offers high diagnostic accuracy in the characterization and detection of FLLs in the non-cirrhotic liver, comparable to CT and MR [115]. Due to expanding recognition of UCA benefits in the liver, CEUS has been added to LI-RADS, the liver imaging reporting and data system that

sets practice standards for virtually all departments that offer advanced liver imaging in North America and beyond.

iii. Newer applications.

UCA benefits are expanding beyond echocardiography and liver imaging as newer applications emerge. For example, UCAs are now showing benefits when used to:

- Evaluate kidney disease and characterize solid masses, cystic lesions, and infections within transplanted kidneys. These masses often present as indeterminate on CT and/or MR. Since UCAs are not nephrotoxic, their use is especially important for patients with compromised renal function and a single kidney [18, 21, 92].
- Predict and diagnose pancreatic cancer, a deadly tumor which is well visualized and confirmed with CEUS [116, 117].
- Monitor and evaluate chronic inflammatory bowel diseases (IBD) including Crohn's disease and ulcerative colitis. The increasing incidence of IBD in pediatric and young adult patients make CEUS especially valuable [118-124].
- Evaluate gallbladder pathology, with excellent detection of both mural inflammatory and neoplastic disease [125, 126].
- Detect and assess residual or recurrent tumors and characterize the geographic patterns of recurrence [13, 14, 127].
- Map sentinel lymph nodes in breast cancer patients allowing for preoperative identification of lymphatic vessels and potential recipient veins [128, 129].
- Provide secondary surveillance post-therapy in lieu of CT and MR, which are not suitable options because they do not offer sufficient resolution [13, 14].
- Identify vulnerable carotid plaque associated with risk of rupture and cardiovascular events [54-57]. Unlike MR, CEUS allows for real-time assessment, higher temporal resolution, wider accessibility, cost-efficiency, bedside applicability and improved patient comfort – making CEUS an efficient and reliable tool for early identification of vulnerable plaques in patients at risk for stroke, and for serial examinations [130].
- Image patients with known or suspected cardiac shunts [131].

- Monitor patients with endovascular aortic stents, which require regular evaluation throughout their existence [132].
- Study varied pediatric pathology, as extensively reported in the literature [119, 133-151].
- Monitor the effectiveness of cancer therapy and other disease treatments [152, 153].
- Evaluate musculoskeletal pathology by assessing tissue microperfusion, inflammation, vascularity, and perioperative complications, including treatment-related changes [154, 155].
- Improve image-guided biopsy and interventional procedures by identifying viable, vascularized tissue and lesions that are inconspicuous on conventional ultrasound or CT, and by providing real-time guidance for needle or ablation-device placement [156, 157].

Additional innovative UCA applications promise to improve the effectiveness of thrombolysis for myocardial infarction [158], allow for targeted molecular imaging [159], and provide a non-viral vector for delivery of cancer drugs and gene therapy [160, 161], among other uses.

iv. Benefits for specific patient populations.

The denominator of the risk-benefit ratio also reflects vital and sometimes life-saving benefits for growing numbers of patients for whom CEUS offers the only diagnostic imaging option that is safe and reliable. For example:

- **Patients with compromised renal function or renal failure.** These patients now comprise an estimated 14% of adults in the U.S. [162], and for them UCAs are the only contrast agents that can be safely and effectively used. UCAs are not nephrotoxic, are not excreted by the kidneys, and can be administered at any level of renal function without the need for renal-function testing; this is particularly valuable when iodinated or gadolinium-based contrast administration is contraindicated or undesirable [14, 93].
- **Pregnant women with serious medical complications.** These patients also have limited options for advanced imaging. In many instances, complications are simply not addressed until the end of gestation. However, CEUS offers a relatively safe imaging option since UCAs do not cross the placenta, and CEUS studies have been performed safely for investigation

of intrapartum problems with excellent results. This includes detection, diagnosis and full management of malignant tumors, both primary and secondary, without resorting to CT or MR [163].

- **Difficult-to-image patients – including increasing numbers of obese patients, patients with severe lung disease or fatty liver disease, and breast cancer patients whose imaging windows are degraded by mastectomy, reconstruction or chest-wall radiation.** CEUS offers an excellent imaging option for many of these patients, who may not be suitable candidates for alternative imaging (including conventional ultrasound).
- **Immobile patients.** Some of the sickest and most vulnerable patients cannot easily be moved to a CT or MR imaging suite. CEUS is often an ideal alternative because it uses portable imaging systems that may be moved to their bedside.
- **Patients in small or rural hospitals, or in economically disadvantaged communities.** These individuals may not have access to on-site CT or MR due to the high cost of installation, maintenance and operation.
- **Patients who cannot afford expensive imaging.** As insurance deductibles increase across geographical regions, many patients simply cannot afford the relatively high cost of a contrast-CT or MR scan.

For a growing number of these patients, CEUS provides an invaluable and potentially life-saving opportunity to access safe, accurate, affordable diagnostic imaging.

v. Benefits for health care systems.

UCAs also offer important benefits for health care systems, as well as individual patients. For example:

- By providing a definitive up-front diagnosis, CEUS may lower costs associated with unnecessary procedures and downstream testing, reduce delays in accessing MR and CT, accelerate the initiation of appropriate therapy, avoid complications, reduce hospitalization time, and improve the efficiency of health care delivery [1, 24, 25, 164-166].
- In echocardiography, a nondiagnostic echocardiogram generally leads to additional procedures such as transesophageal echocardiograms, nuclear

stress tests, cardiac MR, catheterization, etc. – significantly increasing risk, time, inefficiencies and related costs [67].

- In patients recently hospitalized for acute myocardial infarction, CEUS was associated with reduced downstream testing (including coronary angiography and non-stress imaging) and decreased costs of care, with no difference in days alive at home or readmission rates [25].
- One recent study showed an almost 50% reduction of downstream CT and/or MR examinations in pediatric patients following CEUS [83].
- Studies have attempted to estimate the cost savings associated with CEUS. Estimated savings from routine use of UCAs in stress echocardiography - \$238 per patient [165]; from reduced admissions from the Emergency Department - ~\$900 projected per patient [166]; and, in a cost-benefit analysis of contrast use in technically difficult echocardiograms, a net savings of \$122 per patient [1]. UCA use has also been associated with lower total costs of care in outpatients [25].
- Since UCAs do not contain iodinated dye or gadolinium, they do not present a risk of nephrotoxicity or deposition of contrast material in the brain [88] -- which can increase healthcare costs associated with related complications.
- CEUS avoids exposing patients and staff to ionizing radiation, which can increase an individual's risk of cancer (and related costs).
- CEUS utilizes ultrasound equipment that may be purchased at a fraction of the cost of CT and MR machines.
- Since ultrasound equipment is portable and widely-available, CEUS expands patient access to advanced imaging for many patients -- especially where MR or CT scanners are not available or cannot be accessed in a timely fashion.
- CEUS offers a patient-friendly, non-intimidating imaging experience without the need for sedation or anesthesia, reducing the time, cost and risk associated with these procedures. This benefits patients of all ages and across clinical settings [87, 134].

As the clinical and systemic benefits of UCAs expand, the denominator of the risk-benefit ratio more clearly shows that any risk of a rare reaction is outweighed by these benefits.

4. Precedent: Removal of boxed warnings when scientific evidence shows risk is less severe than previously thought.

a. Removal without new clinical trials.

The FDA is not compelled to require new randomized clinical trials before removing a boxed warning. Indeed, in November 2025, the FDA initiated removal of certain boxed warnings for menopausal hormone replacement therapy (HRT) without requiring new clinical trials. The evidence consisted of a comprehensive review of the current scientific literature reflecting a range of study designs and utilization data, an expert panel, and a public comment period. In addition, the women's health community had raised concerns that, because of the boxed warnings, physicians were not prescribing HRT drugs for patients who would derive benefits from them. Based on this data and input, the agency informed application holders it was requesting labeling changes to provide current, accurate and balanced information about the benefits and risks of HRT drugs so women, in consultation with their healthcare providers, can make the best decisions for their health, ending more than two decades of fear and misinformation regarding HRT.

The FDA's historic decision expressly determined that the weight of current evidence overcame outdated interpretations of early Women's Health Initiative (WHI) findings, which overstated risks in older women [167-169]. In explaining its decision to remove the "black box," the FDA stated:

Women may be under-utilizing approved therapies that can alleviate menopause symptoms and improve women's health because of ... "black box" warnings about the risks associated with these drugs that the agency is removing. ...

The FDA concluded that, for healthy women under 60 (or within 10 years of menopause onset), the benefits of systemic HRT typically outweigh the risks. The agency did not remove the boxed warning for endometrial cancer for systemic estrogen-alone products.

b. Clinical trial-driven removal pathway

Other boxed warnings have been removed following examination of new data derived from clinical trials. For example, in August 2020, the FDA removed a boxed warning about amputation risk from the diabetes medicine canagliflozin (marketed as Invokana, Invokamet and Invokamet XR) and moved language addressing amputation risk to the Warnings and Precautions section of the product labels [170]. Of note, the FDA cited enhanced benefits associated with new uses, along with favorable safety information showing reduced risk – particularly when appropriately monitored. In December 2016, the FDA removed a boxed warning from the label of varenicline (Chantix), a smoking

cessation drug [171]. And, in November 2013, the FDA reversed a boxed warning on the labels of rosiglitazone (Avandia, Avandamet and Avandaryl) ¹², Type 2 diabetes drugs [172]. The FDA acknowledged that the relevant studies did not completely eliminate scientific uncertainty about the cardiovascular safety of the product -- but did substantially reduce the agency's level of concern. The agency also acknowledged its responsibility to “reflect the most current scientific knowledge about the risks and benefits” of the drug [172].

5. **FDA standards**: Insufficient basis for mandating boxed warnings for UCAs.

Boxed warnings are the most stringent safety warning the FDA can require. They are intended to call attention to the most serious risks that would be **out of proportion** with the potential benefits of the product. According to 21 CFR § 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 2011 Guidance for Industry explains that boxed warnings are to be used to highlight

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 the drug.

(Emphasis added) [173]. Alternatively, boxed warnings may be used to address a serious adverse reaction that may be prevented or reduced in frequency by appropriate use (e.g., patient selection, careful monitoring, avoiding certain concomitant therapy, addition of another drug or managing patients in a specific manner, avoiding use in a specific clinical situation). A third “black box” rationale involves products approved with restricted access.

These standards do not support the continued requirement of UCA boxed warnings. The totality of current UCA safety data [6, 7, 11, 12, 22, 23, 31, 33, 34, 36-46] now show that:

- The risk of idiosyncratic anaphylactoid reactions associated with UCAs is rare [29].
- CARPA reactions tend to be mild and may occur with other drugs and agents, including nonsteroidal anti-inflammatory drugs and analgesics that are commonly prescribed and are not subject to a boxed warning [84].
- Risk associated with UCA use is lower than the risks associated with similar contrast media that do not have boxed warnings [30, 31].

¹² Avandia prescribing information still carries a boxed warning for congestive heart failure.

- Risk can be ameliorated through dilution and slow administration of UCAs [31] and can be managed through standardized safe laboratory practice identified in the literature [8, 85].

Considered in the context of the significant clinical benefits of UCA use, rare risks associated with UCA use are more appropriately addressed in the WARNINGS and PRECAUTIONS section of each label.

6. Public health concerns: The UCA “black box” deters clinically-appropriate use of safe, beneficial, cost-effective technology.

Over-use of boxed warnings may dilute their impact and undermine trust in the communication of serious and disproportionate risk. Boxed warnings are intended to impact prescribing practices, and data show a precipitous drop in UCA utilization immediately following the imposition of boxed warnings in 2007 [174]. Similar effects have been observed with other drugs [175].

In the shadow of boxed warnings, UCA growth has progressed at a slower pace when compared to potential need and benefit [174]. Although 10%-20% of standard echocardiograms and 33% of stress echocardiograms are considered sub-optimal and non-diagnostic, UCAs were used in only 6.8% of the cardiac ultrasound examinations performed 2018-2022 [25, 71, 73]. Underutilization is of particular concern for critically ill hospitalized patients who derive the most significant benefit [29], and for patients without access to alternative options for advanced imaging. Removal of the boxed warnings would lift a significant deterrent to the clinically-appropriate use of safe, reliable, and potentially life-saving CEUS imaging technology.

Conclusion.

Petitioner respectfully requests the FDA to remove the "black box" from UCA product labels and to move appropriate warnings regarding uncommon cardiopulmonary risk to the WARNINGS and PRECAUTIONS sections of each label. Drug labels should evolve as new information modifies our understanding of safety and benefits; in fact, 21 CFR § 201.56 (a) (2) requires that labeling “must be updated when new information becomes available that causes the labeling to become inaccurate, false, or misleading.”

Current safety data convincingly demonstrate that the clinical benefits of UCAs far outweigh the exceedingly rare risk of an idiosyncratic adverse reaction. Removal of the “black box” would align with precedent and bring UCA labeling into line with labels for other imaging agents, ending a double regulatory standard that distorts perception of relative risk. Ultimately removal of the UCA “black box” will further the public interest by providing more reliable information on which health care decisions are based.

C. Environmental Impact

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

D. Economic Impact

The requested action is not likely to impact the cost of UCAs to industry, government, or consumers. Furthermore, there is no reason to believe the removal of the boxed warning will affect: (1) productivity of wage earners, businesses, or government; (2) competition; (3) suppliers of important materials, products or services; (4) employment; or (5) energy supply or demand.

E. Certification

The undersigned certify that, to the best of their knowledge and belief, this Citizen 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 Petitioner.

Respectfully submitted,

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EXHIBIT A
Boxed warnings: Definity

WARNING: SERIOUS CARDIOPULMONARY REACTIONS

Serious cardiopulmonary reactions, including fatalities, have occurred uncommonly during or following perflutren-containing microsphere administration. Most serious reactions occur within 30 minutes of administration.

- Assess all patients for the presence of any condition that precludes DEFINITY administration. (4)
- Always have resuscitation equipment and trained personnel readily available. (5.1)

FULL PRESCRIBING INFORMATION

WARNING: SERIOUS CARDIOPULMONARY REACTIONS

Serious cardiopulmonary reactions, including fatalities, have occurred uncommonly during or following perflutren-containing microsphere administration. Most serious reactions occur within 30 minutes of administration.

- Assess all patients for the presence of any condition that precludes DEFINITY administration [see *Contraindications (4)*].
- Always have resuscitation equipment and trained personnel readily available [see *Warnings and Precautions (5.1)*].

EXHIBIT B

Boxed warnings: Lumason

WARNING: SERIOUS CARDIOPULMONARY REACTIONS

See full prescribing information for complete boxed warning

Serious cardiopulmonary reactions, including fatalities, have occurred uncommonly during or following the injection of ultrasound contrast agents, including sulfur hexafluoride lipid microspheres (5.1). Most serious reactions occur within 30 minutes of administration (5.1).

- Assess all patients for the presence of any condition that precludes administration (4).
- Always have resuscitation equipment and trained personnel readily available (5.1).

FULL PRESCRIBING INFORMATION

WARNING: SERIOUS CARDIOPULMONARY REACTIONS

Serious cardiopulmonary reactions, including fatalities, have occurred uncommonly during or following the injection of ultrasound contrast agents, including sulfur hexafluoride lipid microspheres *[see Warnings and Precautions (5.1)]*. Most serious reactions occur within 30 minutes of administration *[see Warnings and Precautions (5.1)]*.

- Assess all patients for the presence of any condition that precludes administration *[see Contraindications (4)]*.
- Always have resuscitation equipment and trained personnel readily available *[see Warnings and Precautions (5.1)]*.

EXHIBIT C

Boxed warnings: Optison

WARNING: SERIOUS CARDIOPULMONARY REACTIONS

See full prescribing information for complete boxed warning.

Serious cardiopulmonary reactions, including fatalities, have occurred uncommonly during or following perflutren-containing microsphere administration. Most serious reactions occur within 30 minutes of administration (5.1).

- Assess all patients for the presence of any condition that precludes OPTISON administration (4).
- Always have resuscitation equipment and trained personnel readily available (5.1).

FULL PRESCRIBING INFORMATION

WARNING: SERIOUS CARDIOPULMONARY REACTIONS

Serious cardiopulmonary reactions, including fatalities, have occurred uncommonly during or following perflutren-containing microsphere administration. Most serious reactions occur within 30 minutes of administration *[see Warnings and Precautions (5.1)]*.

- Assess all patients for the presence of any condition that precludes OPTISON administration *[see Contraindications (4)]*.
- Always have resuscitation equipment and trained personnel readily available *[see Warnings and Precautions (5.1)]*.

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