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UPDATED CITIZEN PETITION: Removal of "black box" from ultrasound contrast agent ("UCA") warnings

I. Introduction

The International Contrast Ultrasound Society ("ICUS") is a not-for-profit grassroots medical society that is dedicated to advancing the safe and appropriate use of contrast enhanced ultrasound ("CEUS") imaging to improve patient care and save lives. ICUS members include physicians, nurses, sonographers, scientists, other medical and ultrasound professionals, and members of the general public. Physician members represent a broad range of medical specialties including cardiology (echocardiography), radiology (body imaging including liver and kidney), pediatrics, vascular imaging, internal medicine, gastro-intestinal medicine, emergency medicine, intensive care, obstetrics and gynecology, and others.

CEUS is an enhanced form of diagnostic ultrasound imaging that utilizes UCAs (sometimes also known as "ultrasound enhancement agents" or "UEAs") to improve the functionality, clarity and reliability of ultrasound scans, thereby helping physicians more accurately diagnose and treat medical conditions and monitor therapy. UCAs are safely and routinely used by physicians throughout the world.

The FDA first mandated boxed warnings on UCA labels in 2007. A boxed warning (or "black box") is the strongest warning required by the FDA and signifies a significant risk of a serious or even life-threatening reaction that would be out of proportion with the potential benefits of the product. The UCA boxed warnings followed spontaneous reports of a small number of serious adverse events ("SAEs") that occurred after UCA administration. However, the reported SAEs were not contemporaneously adjudicated and some were later attributed to underlying medical conditions and/or other medication. Since 2007, peer-reviewed publications have consistently shown that UCAs are exceedingly safe, efficacious and save lives. (1)

In response to the growing body of compelling safety and efficacy data, the FDA has narrowed UCA boxed warnings and contraindications, approved a new UCA, and approved the use of CEUS for

new indications and new patient populations including children. At present, the boxed warning on all three FDA-approved UCAs is limited to the stated risk of “serious cardiopulmonary reactions, including fatalities.” (2-4)

Since the FDA’s most recent and appropriate actions on UCA product labels, the body of relevant scientific literature has continued to mature and now convincingly shows that UCAs are among the safest diagnostic imaging products available. (1,5-23) In light of these overwhelming safety data, what remains of the warning inside the “black box” cannot be considered evidence-based. Indeed, the continued existence of the “black box” may actually harm patients by deterring judicious UCA use in those most likely to derive a benefit -- including critically ill hospitalized patients. (1)

Accordingly, in September 2018, the undersigned, on behalf of ICUS, submitted a Citizen Petition under §§ 502 and 505 of the Federal Food, Drug & Cosmetic Act (21 U.S.C. §§ 352 and 355; “FDCA”). The Petition respectfully requested that the Commissioner of Food and Drugs (the “Commissioner”) remove the boxed warnings from UCA product labels. The Petition also supported continued inclusion of appropriate warnings in the Warnings and Precautions section of UCA labels, without a “black box.” A decision is pending.

The purpose of this Updated Citizen Petition is to provide additional references promulgated since the 2018 ICUS submission so that the Commissioner will have the benefit of the latest available information. This Updated Citizen Petition also calls attention to expanded clinical experience with UCAs globally -- including beneficial uses of UCAs for imaging patients suffering from the novel coronavirus. (24) ICUS respectfully requests that the Commissioner consider this Updated Citizen Petition in place of the document submitted in 2018.

We appreciate and share the FDA’s commitment to the best interests of patients. We also recognize that removal of a “black box” requires clinical evidence that risks are less severe than previously thought. This Petition will provide that evidence.

We also note that, following the initial ICUS submission in 2018, virtually every major ultrasound organization, along with numerous individual CEUS experts, filed their own statements with the agency in support of the ICUS Petition and removal of the “black box” from UCA product labels. To our knowledge, not a single statement was submitted in opposition to the ICUS Petition or in favor of retention of the “black box.” A sample of these uncontroverted expert assessments will illustrate the widespread support for the actions herein requested:

- 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.” (25)
- 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.” (26)

- 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.” (27)
- 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.” (28)
- 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.” (29)
- 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.” (30)

II. Support for Actions Requested

ICUS respectfully requests the Commissioner to remove the boxed warning from UCA product labels. In support of this request, ICUS will demonstrate that:

- a) The risk-benefit ratio for UCA use has dramatically changed since 2007, when the “black box” was first mandated. Newer scientific data now consistently show that UCAs are extremely safe, and expanded uses in larger patient populations have extended the clinical benefits of UCAs. (31-33)
- b) Boxed warnings on UCAs deter patient access to safe, real time diagnostic information and therefore have serious deleterious implications on the health of the American public.
- c) Precedent for removal of a “black box” has been established where new scientific evidence demonstrates that risks are less severe than previously thought.
- d) The UCA boxed warnings do not meet the requirements of the FDA’s guidance and standards, which support the use of boxed warnings in limited circumstances, e.g., as where the risks of a product are not in proportion to its potential benefit.
- e) The black box warning for UCAs disregards the FDA’s policy of encouraging innovation and cost savings.

III. Background

A. CEUS and UCAs, Generally

CEUS is a diagnostic imaging tool that uses UCAs to enhance conventional ultrasound scans. UCAs are comprised of liquid suspensions of gas-filled microbubbles that may be injected intravenously during a diagnostic ultrasound scan. UCAs are biocompatible, do not contain radioactive dye or material, present no known risk of brain deposits and are not known to damage the kidney. They are metabolized and expelled from the body, primarily through the lungs, within minutes. (2-4)

UCAs often improve the clarity and reliability of ultrasound images and produce exquisite images of tumors and organ blood vessels in adults and children. (5) This enables the use of CEUS for making a more accurate initial diagnosis (34), applying more appropriate treatment protocols and monitoring therapy. High resolution CEUS images of the cardiovascular system can dramatically improve the detection of cardiac abnormalities and stratify risk of heart attack or stroke. In addition, CEUS images of the liver, kidney, prostate, breast and other organ systems help physicians identify, characterize and stage tumors and other medical abnormalities.

CEUS scans are performed without any ionizing radiation and often allow for diagnoses that otherwise would require the use of a CT or MR scan. However, unlike CT and MR, CEUS utilizes portable and relatively low-cost equipment, and can be offered in a variety of clinical settings -- including the intensive care unit and outpatient clinics. In addition, CEUS provides real time diagnostic information that can speed access to appropriate therapy. Studies and extensive clinical experience show that CEUS can help avoid unnecessary downstream tests, lower overall health care costs, reduce the length of hospital stays by speeding time to diagnosis and treatment, improve the efficiency of health care delivery, change patient outcomes and save lives. (33,35)

UCAs also allow physicians 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 suboptimal or uninterpretable due to inadequate resolution, (36) 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 left ventricular assist devices ("LVADs"). (35,37-40) When UCAs are used to salvage these non-diagnostic echocardiograms, patients are often spared the expense, risk and inconvenience of redundant downstream testing.

UCAs also may be quite useful for reliably and expeditiously imaging patients suffering from the novel coronavirus. Time is of the essence in performing diagnostic procedures in these highly vulnerable patients, and conventional ultrasound often produces poor quality images of their heart chambers and lungs. Meanwhile, alternative imaging tools such as CT or MR require transporting these patients through the hospital, potentially increasing time to diagnosis and exposure of health care workers. CEUS may improve the quality of conventional ultrasound images, may be performed at bedside, provides real time diagnostic information, and generally saves time and reduces unnecessary exposure. CEUS experts recommend further studies to confirm the anticipated clinical benefits of UCAs for imaging Covid-19 patients. (24)

B. UCA Regulatory Background

Pursuant to the Commissioner's authority under 21 C.F.R. §§ 10.30 and 201.57(c)(1), a boxed warning is currently included on the labels of the three UCAs that are commercially available in the United States: Optison, Definity, and Lumason. (2-4) Each of these products is approved for use in patients with suboptimal echocardiograms to opacify the left ventricle and to improve the delineation of the left ventricular endocardial borders. In addition, Lumason is approved for use in ultrasonography of the liver in adult and pediatric patients, and in ultrasonography of the urinary tract in pediatric patients.

As noted above, the FDA first mandated boxed warnings on UCAs in October 2007. This action was largely based on reports of four patient deaths and approximately 190 other serious cardiopulmonary reactions that were temporally related, but not clearly caused by, UCAs. At the time, Optison and Definity were the only two FDA-approved UCAs. (5)

The boxed warning for each product advises that "serious cardiopulmonary reactions" may occur during or following the injection of UCAs.

For Definity and 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 [see WARNINGS AND PRECAUTIONS (5.1)]. Most serious reactions occur within 30 minutes of administration.

- Assess all patients for the presence of any condition that precludes [DEFINITY®/Optison] administration [see CONTRAINDICATIONS (4)].
- Always have resuscitation equipment and trained personnel readily available.

For 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.

Since 2007, ICUS and other stakeholders have advocated for modifications of the UCA labels. These efforts began in Fall 2007 when, in response to the FDA's action, 160 cardiologists and radiologists from around the world sent a letter to the FDA stating that the boxed warnings do not reflect the established record of safety and efficacy for UCAs, or the potential risks of alternative diagnostic procedures and inaccurate non-diagnostic ultrasound scans. In December of 2007, FDA staff met with the lead authors, and several investigator-initiated safety studies were soon published. In May of 2008, the FDA modified and reversed certain contraindications and warnings, stating that "the benefits from the diagnostic information ... may outweigh the risk for serious cardiopulmonary reactions, even among some patients at particularly high risk for these reactions."

Following the publication of additional favorable safety data, ICUS in 2011 filed a citizen petition with the FDA requesting the removal of boxed warnings and modification of warnings on UCAs. In October 2011, the FDA announced additional revision of the product labeling for UCAs, including deletion of a previously-mandated 30-minute monitoring period after UCA administration in patients with certain cardiac conditions. (41)

In September of 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"). The ICUS presentation 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. (31,32)

In 2016, the FDA approved a third UCA, Lumason, for use in liver and pediatric imaging, and removed the cardiac shunt contraindication from all UCA labels. In May 2017, ICUS presented an additional professional society briefing for the FDA Division of Medical Imaging Products, highlighting new safety data and the use of CEUS to image other organs "off-label."

Since the FDA's actions in 2016, considerable additional UCA studies have been published and describe UCA use in diverse clinical settings and patient populations, including adults who are critically ill and children. These new publications consistently show that UCAs are safe and beneficial. These findings will be more fully discussed below.

IV. Statement of Grounds

A. *Scientific Data Now Demonstrate a Favorable "Risk-Benefit" Ratio That Does Not Justify a "Black Box"*

A growing body of scientific research now demonstrates that UCAs are exceedingly safe. (1) In addition, their expanding clinical benefits reflect proven efficacy in an increasing number of new indications and new populations, in some cases with equivalent or greater efficacy than alternative diagnostic imaging modalities. (1,5-23,32,42-45)

These compelling developments support a new understanding of both the numerator and denominator of the risk-benefit ratio, making it clear that the benefits of UCAs far outweigh any risk of an exceedingly rare idiosyncratic reaction. Current safety and efficacy data also demonstrate that the risk-benefit ratio is inconsistent with the FDA's standards for mandating boxed warnings to highlight the possibility of 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." (46)

I. The Numerator: New Safety Data

Since the FDA first mandated the “black box” on UCA product labels, a growing body of scientific evidence has demonstrated that UCAs have an excellent safety profile in an expanding variety of clinical settings. Subjects have included outpatients, hospitalized patients (including the critically ill), patients with serious cardiopulmonary conditions and intra-cardiac shunts, and patients with liver tumors and kidney disease. Subjects also include adults and children. (1,5-23) (6-23,32,42-45)

These UCA studies consistently show that any risk of a serious adverse event is exceedingly low -- with rare allergic and anaphylactoid reactions found in approximately 1:10,000 patients. (1) Complement Activation Related Pseudo Allergy (or “CARPA”) reactions may be associated with UCAs as well as 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. (47) We are unaware of any data supporting the current UCA warning of increased risk in patients with unstable cardiopulmonary conditions. (1)

The following examples illustrate the impressive UCA safety data developed in recent years:

- Six early safety studies were designed collaboratively between the FDA and UCA manufacturers. No deaths or SAEs occurred in any of the studies, 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. (1)
- A recent large meta-analysis evaluated the use of UCAs in 110,500 patients, and found that the incidence of serious allergic or anaphylactoid reactions immediately after administration of the UCA was estimated at only 0.009% (for serious allergic reactions) and 0.004% (for anaphylactoid reactions). (1,35)
- Newly published guidelines for implementing a liver CEUS program state that, despite concern over rare anaphylactic reactions, “adverse events from liver contrast scanning are low, 0.008% in over 23,000 patients without any deaths reported.” The guidelines also note that because UCAs are vascular agents, they are not nephrotoxic and do not collect in the renal spaces, and they do not carry risks associated with iodized contrast agents used in CT or gadolinium used in MR. (48)
- The safety of abdominal CEUS was also reported in a retrospective study of 23,188 examinations in 28 Italian medical centers. According to Piscaglia et al., there were no fatalities, and only 29 adverse events (0.0086%), two of which were serious. (24) Similarly, no fatalities were associated with UCA administration in a retrospective study of 30,222 patients at a large hospital in China. Adverse events were experienced by 6 patients (0.02%), two of which were serious (0.007%). (43)
- CEUS, when used as a front-line diagnostic imaging tool, changed patient management in 35.5% of patients overall -- with the greatest impact on the care of the sickest patients, 62.9% of whose management was changed. In addition to modifications in medication, UCAs also reduced the use of redundant downstream diagnostic imaging -- which may expose patients to added, unnecessary risk. (35)

- Main et al reported on the use of UCAs in 4,300,966 hospitalized patients included in the Premier Perspective Database, the largest hospital-based comparative database in the USA. Results showed that patients receiving an UCA-enhanced echocardiogram were actually 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. (10)
- Another retrospective study 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. (22) A total of 1,006,381 patients were assessed, and the difference between groups was observed at 48 hours and persisted throughout the hospital stay.
- UCAs have been found to be safe and provide potentially lifesaving diagnostic information in patients with left ventricular assist devices ("LVADs"), who are among the sickest patients. Normal echocardiographic imaging is difficult in some LVAD patients because of the positioning of the device. The use of CEUS improved image interpretation in 83% of these patients, and no adverse events or known side effects were reported during or after the CEUS. In addition, LVAD function was not affected during or after the CEUS. (45,49)
- Another study found no increased risk of death or heart attack associated with UCAs in patients who underwent stress echocardiography. (13)
- Two studies have concluded that UCAs are not associated with any neurological safety signals. (10,12)
- Several studies have also demonstrated that UCAs appear to be safe in patients with pulmonary hypertension. (1)
- Pediatric CEUS safety studies now demonstrate very few adverse events and very rarely SAEs. In addition, pediatric patients are exposed to greater risk from certain downstream tests. Since children are more sensitive to ionizing radiation than adults, and since the cancer risk associated with exposure to ionizing radiation is cumulative over a patient's lifetime, it may be especially important to avoid pediatric CT scans, which are the single largest contributor to medical radiation exposure in the United States. (50) In pediatric patients, CEUS may reduce or replace the need for fluoroscopic exams and CT exams. (31)
- In addition, MRI often requires the use of MRI contrast agents - with yet unknown long-term consequences of their deposition in various organs, particularly the brain. For example, in December 2017 the FDA announced that it is requiring a new class warning and other safety measures for all gadolinium-based contrast agents (GBCAs) for MRI concerning possible links to adverse health effects from gadolinium retention in patients' bodies, including the brain, months to years after receiving these drugs. (51) This is of particular concern in children, whose brains are still developing.
- CEUS is a patient-friendly, non-intimidating imaging technique that does not require sedation or anesthesia, which entail their own adverse events. (50) This, too, can be particularly significant when imaging children.

In addition to these investigator initiated studies, multi-center clinical trials have been performed since 2007 in connection with the April 2016 approval of Lumason. These clinical trials contribute additional compelling evidence of safety. As noted on the Lumason product label, a total of 6,984 subjects were studied and only two reported serious adverse reactions.

II. The Denominator: Expanded Benefits With New Indications and Populations

The denominator of the “risk-benefit ratio” also has changed since 2016 and now independently supports the conclusion that any risk associated with UCAs is far outweighed by the compelling benefits of their use in an expanding range of clinical settings. Expanded evidence of UCA benefit is supported by new clinical indications in new populations, reduced contraindications and efficacy data, some of which overlap with the safety literature discussed above. Further, we note that an estimated 10% of patient deaths are the result of diagnostic errors (52,53) and, to the extent UCA use improves the accuracy of a diagnosis and leads to implementation of appropriate therapy, lives will be saved.

Examples of expanding CEUS benefits include the following:

- UCAs are now used in the United States to image the liver and characterize focal liver lesions. (54) The addition of CEUS to liver imaging protocols improves interpreter accuracy by 88% over a baseline of 35% for gray-scale sonography alone. (48)
- In fact, a May 2020 report concluded that CEUS has high diagnostic accuracy in the characterization and detection of focal liver lesions (FLL) in the non-cirrhotic liver, comparable to CT and MR. The report also stated that CEUS is generally useful for liver biopsy and ablation guidance. (55)
- Dynamic CEUS may be used to predict hepatocellular carcinoma (“HCC”) and differentiate it from non-HCC malignancies and benign nodules. In this context, CEUS is considered a viable problem-solving tool when MR is indeterminate. In addition, when LI-RADS LR-5 category protocols are used, CEUS may eliminate the need for biopsy to confirm a HCC diagnosis. (56)
- CEUS also may play a vital role in ablative therapy and secondary surveillance of HCC, and may accurately detect residual or recurrent tumor and characterize the geographic pattern of recurrence. (57)
- CEUS is of great value in evaluating disease within native kidneys, and also may be used to characterize solid masses, cystic lesions, and infections within transplanted kidneys. Lack of nephrotoxicity of UCAs makes their use particularly appealing for patients with compromised renal function and a single kidney. (58)
- CEUS imaging of carotid intraplaque neovascularization is now used to predict cardiovascular events. (59,60)
- UCAs are also used in pediatric imaging (31) (42) and in patients with known or suspected cardiac shunts, comprises 10-35% of the population. (61)

- CEUS can be used in difficult to image patients, including those who are obese, have breast cancer or severe lung disease, or who have other physical impediments that make alternative imaging (including conventional ultrasound) challenging. (35)
- CEUS has been shown to save the lives of critically ill patients in the intensive care unit. (22)
- CEUS offers multiple advantages over alternative forms of imaging and reduces fluoroscopic exams, CT exams (31) and MRI. In fact, one recent study showed an almost 50% reduction of downstream CT and/or MRI examinations in pediatric patients after the introduction of CEUS. (42)
- CEUS offers a patient-friendly, non-intimidating imaging experience that does not require sedation or anesthesia; this can be especially important for pediatric patients. (42,50,62,63)
- By utilizing portable and widely available ultrasound equipment and by providing real-time diagnostic information, CEUS expands access to diagnostic imaging, speeds the introduction of appropriate therapy, reduces hospitalization time, and improves the efficiency of health care delivery. (33)
- By reducing the need for downstream testing, CEUS reduces overall health care costs and improves outcomes without exposing patients to ionizing radiation or increasing the risk for nephrotoxicity.

B. The “Black Box” Deters Appropriate Use and Impacts the Public

The FDA has determined that the addition of a boxed warning has had varying effects on prescribing practices, and the agency is about to commence a survey to better understand how health care providers actually use boxed warning information. (64) Nevertheless, it is clear that a boxed warning is intended to alert health care providers and their patients to the most serious level of risk, and ICUS, other ultrasound professional societies and individual CEUS experts believe that the boxed warnings on UCA product labels have unduly deterred use.

Shortly after boxed warnings were added to UCA product labels in 2007, CEUS precipitously declined as a percentage of total echocardiography studies. (65) And, despite more recent increases in CEUS, it remains an underutilized imaging modality as evidenced by the discrepancy between the estimated number of non-diagnostic ultrasound scans and the actual use of CEUS. For example, in the context of cardiac CEUS, between 10%-20% of standard echocardiograms and 33% of stress echocardiograms are considered sub-optimal and non-diagnostic. (36) However, UCAs are used in only 5.5% of an estimated 32 million ultrasound scans performed in the USA in 2016. (65)

Removal of the boxed warnings on UCA product labels would lift a significant impediment to the appropriate use of safe, reliable, and potentially life-saving CEUS imaging technology.

C. Precedent for Removal of a “Black Box” When New Evidence Demonstrates Safety

The FDA will remove a “black box” when clinical evidence demonstrates that risks are less severe than previously thought. For example, in November 2013, the FDA reversed the “black box” on a diabetes drug known as rosiglitazone (marketed as Avandia, Avandamet and Avandaryl) after new

evidence suggested that there was in fact no increased risk of heart attack or death, as previously thought. Similarly, on August 26, 2020, the FDA announced removal of the boxed warning about the risk of leg and foot amputations for canagliflozin (marketed as Invokana, Invokamet and Invokamet XR) based on new data demonstrating safety.

1. Rosiglitazone

The rosiglitazone “black box” reversal was based on new data from a large, long-term clinical trial and re-evaluation of the relevant data. In the clinical trial, patients treated with rosiglitazone were compared to those treated with alternative diabetes drugs (metformin and sulfonylurea). Rosiglitazone patients experienced fewer deaths from a cardiovascular cause, from a stroke, and from a heart attack; fewer nonfatal strokes; and fewer deaths from any cause. Importantly, the new data failed to confirm the signal of increased risk found in the meta-analysis of clinical trials that triggered the “black box” -- coincidentally mandated in 2007. (66)

In removing the rosiglitazone black box, 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. (66) Further, the agency correctly focused on its responsibility to “reflect the most current scientific knowledge about the risks and benefits” of the drug” (66), without regard to whether the removal would actually impact utilization. The fact that rosiglitazone utilization never rebounded is not just “beside the point” from a safety and efficacy perspective -- it also may be explained by persistent online misinformation that continued to reference the “black box,” a lack of marketing and media coverage of removal relative to coverage of the initial safety concerns, and potentially reduced corporate motivation to invest in correcting misinformation since the product was nearing the end of its patent life. (67)

2. Canagliflozin

The boxed warning on canagliflozin was mandated in 2017 based on the FDA’s determination that the associated risk of amputations was very serious in relation to the potential benefit of the drug, initially approved for use with diet and exercise to lower blood sugar in adults with Type 2 diabetes. The FDA later approved canagliflozin for new indications based on clinical trials showing additional benefits related to the heart and kidney.

In determining that the Boxed Warning should be removed, the stated that the new uses “show significantly enhanced benefit of this medicine,” and that safety data derived from the clinical trials “also suggests that the risk of amputation, while still increased with canagliflozin, is lower than previously described, particularly when appropriately monitored.” (68) Under these circumstances, the agency determined that the amputation risk should be described in the Warnings and Precautions section of the product label.

3. UCAs

As indicated above, since the UCA boxed warnings were mandated in 2007, the safety and benefits of UCAs have been convincingly demonstrated in numerous investigator initiated studies as well as in clinical trials. In addition, new uses have been approved since 2007 and still other uses have been described in peer reviewed publications (58) and supported by professional society guidelines. (69,70) This strong record of safety and expanding benefits calls to mind the changing risk-benefit ratios that warranted removal of boxed warnings from product labels of rosiglitazone and canagliflozin.

D. “Black Box” on UCAs is Inconsistent With the FDA Standards

Boxed warnings are intended to prominently call attention to the most serious risks associated with medical products and are only appropriate in limited circumstances which do not include UCAs. These circumstances are limited because over-use of boxed warnings would dilute their overall impact and undermine trust in their representation of serious, disproportionate risk.

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.) (46) 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 would not seem to require a boxed warning for rare, idiosyncratic reactions which have no dose-response relationship.

Based on the totality of UCA safety data now available, it is clear that the boxed warnings on UCAs fail to meet the FDA’s standards. As noted above, the risk of idiosyncratic anaphylactoid reactions associated with UCAs is rare and occurs in only one in ten thousand patients. (1) In addition, the incidence of serious allergic or anaphylactoid reactions immediately after UCA administration was only 0.009% (for serious allergic reactions) and 0.004% (for anaphylactoid reactions). (44) 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. (1)

Further, at the time the boxed warnings were mandated, only two UCAs were FDA-approved and their indications were limited to cardiac imaging. Since then, a third UCA has been approved and benefits are now being derived from CEUS imaging of the liver, kidneys and other organ systems in adults and children, including patients with known or suspected intra-cardiac shunts. Taken together, these developments significantly alter our understanding of the risk-benefit ratio associated with UCA use and show that the “black box” on UCA product labels is out of sync with current data and experiences.

E. “Black Box” Disregards the FDA’s Move Toward Encouraging Innovation and Cost-Saving

In its 2018 strategic policy roadmap, the FDA expressed a commitment to leveraging innovation to improve health care, broaden access, and advance public health; these goals were identified as a key priority of the agency.(71) Indeed, the FDA’s core mission is to protect public health, which includes ensuring that products are properly labeled to facilitate appropriate use.

CEUS is often equivalent to, and is sometimes superior to, more costly diagnostic imaging tools such as CT and MR. CEUS utilizes ultrasound equipment that may be purchased at a fraction of the cost of CT and MR machines. And, by reducing the need for downstream testing, CEUS reduces overall health care costs associated with the imaging procedure. CEUS also avoids exposure to ionizing radiation and risk of nephrotoxicity and deposit of contrast material in the brain -- all of which potentially increase health care costs associated with related complications. In addition, newer studies indicate that by providing real-time diagnostic information, CEUS may improve health care efficiencies.

Unfortunately, although CEUS is a reliable and accurate diagnostic tool, the current boxed warning deters appropriate use and should be removed. Removing the boxed warning for UCAs would encourage more widespread adoption of this innovative technique that can save lives and healthcare costs.

V. Conclusion

Product labels should and do evolve as new information modifies our understanding of product safety and benefits. Since 2007, the body of scientific literature relating to UCAs has matured, producing compelling new safety data through a combination of investigator initiated studies and clinical trials. This new information, along with expanding clinical applications, provide convincing evidence of the exceedingly favorable risk-benefit profile for UCAs.

To date, the FDA has appropriately responded to the incremental development of new UCA information by downgrading warnings and contra-indications, and approving new indications for expanded population groups. As the FDA concluded as early as May 2008: “the benefits from the diagnostic information ... may outweigh the risk for serious cardiopulmonary reactions, even among some patients at particularly high risk for these reactions.” Since the FDA’s most recent actions on UCA product labels, still more scientific evidence and expanding uses have been developed, and they now convincingly demonstrate that the benefits from the diagnostic information DO outweigh the risk, if any, for serious cardiopulmonary reactions.

Accordingly, it is time to remove the “black box” from these innovative, life-saving diagnostic tools, and include appropriate warnings in the Warnings and Precautions section of each product label. The FDA has removed a “black box” on other products when new clinical evidence demonstrated that the products were safe and any risks were less severe than previously thought. That important precedent clearly applies to the “black box” on UCAs. ICUS and a groundswell of other ultrasound professional societies and CEUS experts overwhelmingly support removal of the “black box,” recognizing the exceptional safety profile of UCAs and their compelling benefits for patient care. Indeed, we are unaware of any clinical evidence of increased risk in patients with unstable cardiopulmonary conditions.

Removing this “black box” will help patients across America access safer, more reliable and more cost-effective diagnostic imaging, while speeding up the introduction of appropriate therapy and saving lives. The public interest -- as well as the FDA's own standards -- demand nothing less.

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

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.

VIII. Certification

The undersigned certifies, that, to the best knowledge and belief of the undersigned, 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,



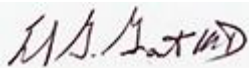
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