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Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

https://www.regulations.gov

Re: Statement supporting repurposing of FDA-approved ultrasound contrast agents for a broader whole-body indication

Introduction

The International Contrast Ultrasound Society 2.0 (“ICUS”) respectfully submits this statement to the U.S. Food and Drug Administration (“FDA”) in response to the agency’s Request for Information regarding "Drug Repurposing for Unmet Medical Needs," dated May 12, 2026, in order to provide support for the repurposing of FDA-approved ultrasound contrast agents (“UCAs”) to help address unmet medical needs across a range of diseases and conditions (1).

ICUS is a grassroots not-for-profit medical society that is dedicated to advancing the safe and appropriate use of contrast enhanced ultrasound (“CEUS”) imaging to improve patient care and outcomes. CEUS is a non-invasive diagnostic imaging modality that uses microbubble UCAs[1] to enhance ultrasound scans -- providing blood flow

[1] UCAs are sometimes also referred to as “ultrasound enhancing agents” or “UEAs.” For purposes of this document, the term ultrasound contrast agent (or UCA) expressly excludes ExEm® Foam, a specialized foam-based UCA approved for assessment of fallopian tube patency, and ICUS does not request approval of ExEm® Foam for whole-body imaging.

information that helps physicians diagnose benign or malignant tumors and assess organ perfusion throughout the body. CEUS is also used to more clearly delineate the blood-tissue border, helping to improve confidence in image interpretation (2-5). CEUS does not expose patients or staff to ionizing radiation or risk of nephrotoxicity, and the safety, efficacy, affordability and convenience of CEUS are well established; additionally, the use of UCAs has been associated with improved diagnostic accuracy, lower rates of downstream testing and procedures, lower costs, and, in some cases, reduced mortality (5-30).

Because of their proven safety, versatility, reliability and cost saving potential, FDA-approved UCAs are ideal candidates for drug repurposing. At present, FDA approvals only cover UCA use in adult liver and cardiac indications, and in certain pediatric indications (31). However, a compelling body of published scientific studies and national and international clinical practice guidelines convincingly demonstrate the broader benefits of using UCAs to address unmet medical needs in the kidney, breast, thyroid, pancreas, spleen, bowel, musculoskeletal system, testicles, uterus and ovaries. UCAs also are beneficial for detecting organ injury following acute trauma, providing guidance in interventional procedures, and monitoring therapy (18,31-35).

This broad range of UCA benefits is not surprising. UCAs are systemic agents that flow throughout the patient's circulatory system and enhance vascular images of organ systems throughout the body. By simply moving the external ultrasound transducer, a clinician can evaluate pathology across organ systems, following disease wherever it may be found. For example, while imaging the liver, a clinician may spot a suspicious lesion in the kidney or spleen; it would be irresponsible not to move the transducer to follow disease, but doing so is not yet FDA-approved. This is clinically illogical and potentially detrimental to patient care.

Action Requested

ICUS urges the FDA to repurpose approved UCAs for broader whole-body use -- without requiring organ-by-organ regulatory submissions and allowing for fast-tracked review with consideration of real-world evidence and data obtained from routine clinical practice (36). The safety of approved UCAs has already been established to the satisfaction of the agency. In addition, as explained more fully below, substantial scientific and clinical evidence, grounded in well-controlled investigations by qualified CEUS experts, strongly supports efficacy across broader uses. Accordingly, approved UCAs meet the FDA's stated criteria for repurposing approved drugs: (1) Compelling scientific

evidence supports effectiveness for whole body use, (2) Dosage and route of administration will be the same, and (3) The safety profile will be comparable.

Unfortunately, the current organ-specific approval process is expensive, burdensome, redundant and clinically illogical. It does not improve our understanding of the risks and benefits of UCAs outside the liver and heart. And, it has the effect of unduly:

- discouraging submissions for new UCA indications;
- depressing CEUS adoption outside the heart and liver;
- restricting physician access to training opportunities; and
- limiting patient access to a safe, affordable, patient-friendly and clinically effective diagnostic imaging modality.

Limited access to whole-body CEUS may be especially concerning for individual patients who cannot undergo contrast-MR or CT – including pregnant patients; obese patients; individuals with fatty liver disease or kidney disease; breast cancer patients with compromised imaging windows; patients in rural hospitals lacking on-site CT or MR; and, increasingly, patients with high insurance deductibles who cannot afford the high cost of contrast-CT or MR studies. Many of these patients have conditions that overlap with the FDA's "priority areas" for repurposing drugs (e.g., metabolic diseases, women's health conditions, rare diseases). And, without access to alternative options, these patients have significant unmet medical needs.

Analysis

1. UCAs are systemic agents with enhancement patterns that are not organ-specific

UCAs are systemic echogenic blood-pool agents comprised of liquid suspensions of gas-filled microbubbles that are smaller than red blood cells. When administered intravenously during an ultrasound examination, the microbubbles flow unimpeded throughout the patient's microcirculation, enhancing ultrasound images of organ systems throughout the body. After several minutes, the UCAs are safely eliminated from the body by exhaling the gaseous core of the microbubbles through the lungs and metabolizing the microbubble shell (lipids or proteins) by the liver and spleen.

Since microbubble UCAs are systemic agents, their enhancement pattens are not organ specific. A single intravenous injection of a UCA will show perfusion of all of the organs in the body, and the choice of organ does not in any way alter the patient risk. Bioeffects are minimal since a very low mechanical index (MI) is used. There is no

evidence or logical basis for believing that there is any difference whatsoever between the safety of UCAs when used to image the liver, heart or other organs.

2. Studies have already demonstrated that UCAs are safe and offer clinical benefits across organ systems

UCAs are among the safest contrast media available, and a large body of scientific evidence demonstrates their excellent safety profile across a variety of clinical settings (8,12,15,16,26-28,37,38). Studies consistently show that any risk of a serious adverse event is exceedingly low, with rare allergic and anaphylactoid reactions (Complement Activation Related Pseudo Allergy ["CARPA"]) found in approximately 1:10,000 patients (15,37), including in contemporary data. Adverse events associated with liver CEUS are similarly low at 0.008% in over 23,000 patients, with no deaths reported (39). Although CARPA reactions may be associated with UCAs, they also occur with other drugs or agents (12,14,15,27,40-43). Mitigation of rare risk may be feasible through dilution, slow administration, and screening (41,44). Importantly, CEUS does not expose patients or staff to ionizing radiation, which increases a patient's cumulative lifetime risk of cancer, and UCAs are inherently safer than contrast agents used to enhance CT or MR scans (43) since:

- UCAs do <u>not</u> contain iodinated dye, which is present in CT contrast agents and which presents a risk of nephrotoxicity; and
- UCAs do <u>not</u> contain gadolinium, which is present in MR contrast agents and which presents a risk of allergic reaction or, in some cases, gadolinium deposits in the brain (the long-term consequences of which are unknown).

The clinical benefits of CEUS are also well established. CEUS sensitivity and specificity are often equivalent to, and sometimes are superior to, contrast-enhanced CT and MR (20). By adding a UCA to a standard ultrasound liver imaging protocol, interpreter accuracy may improve by as much as 88% over a baseline of 35% for gray-scale sonography alone (45). Further, unlike CT and MR contrast agents, UCAs do not leak into interstitial spaces, making them ideal agents for assessing perfusion of tumors and organ systems (46). CEUS often improves detection of residual or recurring cancer cells after treatment and offers an important option for perfusion assessment (47).

When CEUS is used as a front-line diagnostic imaging tool, it often improves patient management and outcomes while lowering healthcare costs (5,6). By providing a reliable diagnosis in real time, in a single setting, CEUS reduces the need for more expensive downstream tests and procedures (5,6,28) improves health care efficiencies and streamlines workflows. In some cases, length of stay is also reduced (6,29). CEUS

also avoids the long waits, often months, to get a CT or MR at many institutions, so diagnosis and treatment initiation may be speedier and more efficient. Additionally, small, portable, mobile, high resolution ultrasound systems may be purchased at a fraction of the cost of CT and MR systems and are significantly more convenient to access than the large, immovable, cumbersome gantry required to house CT and MR scanners. And, since ultrasound equipment is more readily available than CT and MR (48), CEUS can improve patient access to cutting-edge imaging for diverse patient populations including the poor and those who do not have access to advanced, mostly urban medical centers.

Moreover, as mentioned above, for some patients CEUS is the only safe and reliable imaging option available. Those with chronic kidney disease or acute kidney injury may not be candidates for contrast-CT or MR due to the risk of nephrotoxicity – a risk that is not present with CEUS (23) . Similarly, for pregnant patients who may not wish to be exposed to ionizing radiation or other forms of contrast, CEUS may be an ideal imaging option since UCAs do not cross the placenta (49). Some of our sickest and most vulnerable patients cannot easily be moved to a CT or MR imaging suite, whereas CEUS uses portable imaging systems that may be moved to their bedside. For increasing numbers of obese and high BMI patients (50), as well as those with fatty liver disease, CEUS can leverage advances in ultrasound equipment and probes to address challenges involving reduced ultrasound beam penetration, thereby increasing the range of suitable patients for an ultrasound study (51). CEUS is also demonstrably beneficial for surveillance of breast cancer patients whose imaging windows are degraded by mastectomy, reconstruction, or chest-wall radiation (52). Further, as insurance deductibles increase, many patients cannot afford the high cost of alternative imaging options such as CT and MR.

UCA indications outside the liver and heart are widely supported across the clinical, scientific and health care policy ecosystem. National and international clinical practice guidelines reflect a strong consensus in favor of UCA use across multiple organ systems (18,23,45,53). Similarly, a recent consensus statement by 12 ultrasound professional societies supports broader CEUS use (12). Indeed, off-label uses are so well studied and accepted that the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) has published guidelines recommending CEUS for assessing pancreatic masses, the GI tract, spleen, the entire urogenital tract, and much more (54). Additionally, a growing body of scientific literature attests to the safety and efficacy of UCA applications outside the liver and heart (7). In recognition of the importance of off-label as well as approved UCA uses, the Centers for Medicare & Medicaid Services recently doubled payment for all non-cardiac CEUS uses irrespective of the organ imaged, CEUS training across organs was recently added to the National

Education Curriculum (NEC) and CEUS competency was added to the draft CAAHEP accreditation standards for sonography training programs.

3. Limited UCA approvals chill education and stall adoption of uses that are safe and beneficial to patients

While off-label use of approved drugs may be common (55) it is not without significant real-world limitations. FDA approval signifies that a drug is safe and effective *when used as labeled*. Approval gives clinicians and patients confidence that the benefits of a drug outweigh known and potential risks. Unfortunately, limited, organ-specific approvals of UCAs may confuse physicians and their patients by erroneously suggesting that the distribution of contrast is limited to two organs – the liver and the heart -- and that use in other organs is not safe and effective.

Limited UCA approvals also have the effect of chilling the dissemination of factual, evidence-based information about beneficial off-label uses (56). Speakers at CME-accredited educational programs sponsored by industry have been instructed not to discuss off-label uses, essentially requiring that these professional experts ignore important evidence-based indications. Similarly, industry application specialists cannot instruct clinicians on best practices for product-specific off-label administration, optimization, trouble-shooting and confident image interpretation – matters they deal with on a daily basis. This is especially concerning because, unlike CT and MRI, ultrasound is more operator dependent. Without robust product-specific education for off-label uses, CEUS examinations for unapproved indications may be performed poorly and images may not be interpreted correctly, possibly leading to misdiagnoses and jeopardizing optimal patient care.

Additionally, for administrative and compliance reasons, some clinicians and health care facilities are reluctant to perform off-label UCA studies even where doing so is evidence-based, professionally recommended, legal and reimbursed. Administrators may perceive increased clinical risk and legal exposure for novel unapproved uses even though the study would be performed with the same drug used on label for other studies. While a detailed analysis of potential legal liability associated with off-label UCA use is beyond the scope of this statement, we note the perception that the risk of liability may be higher for off-label contrast media use since it is formally outside regulatory boundaries (55). Additionally, use of a contrast agent that the FDA has not stated is safe and effective for a particular use may require the defensive production of “exhaustive information to patients” along with informed consent (55). Consequently, pending approval of a UCA whole-body indication, some clinicians and facilities simply shift patients to contrast-

enhanced CT or MR – studies that are more expensive, more invasive, less available and, in some cases, not capable of providing a definitive study (57).

4. Clinical benefits outside the liver and heart are widely recognized

a) Incidental detection of pathology near the liver

When performing a CEUS examination of the liver, significant pathology may be incidentally identified in a nearby organ. For example, when CEUS is used to characterize a liver mass, metastases may be detected within an adjacent organ such as the kidney or the bowel. A single CEUS exam would optimally assess and characterize the entire pathology. There would be no clinical benefit to stopping the CEUS exam and sending the patient for yet another contrast enhanced exam on CT or MR; in fact, doing so would delay the diagnosis and initiation of appropriate treatment, while unnecessarily increasing costs, risks associated with the added procedure, and patient anxiety.

b) Renal compromise

UCAs are the only effective contrast option for assessing solid organ perfusion in patients with compromised renal function or renal failure – an estimated 15% of adults in the U.S. (58). These patients cannot safely undergo a contrast enhanced CT or MR scan without risk of renal failure; consequently, these patients often receive unenhanced CT or MR scans -- which are often inadequate because the assessment of solid organ perfusion is solely based on the benefits afforded by the differential in tissue enhancement following contrast injection.

UCAs are the only contrast agents that can be safely and effectively used in patients with any degree of renal compromise (18). Peer-reviewed studies show that CEUS produces excellent assessments of organ perfusion without any risk of nephrotoxicity or kidney damage, regardless of the degree of preexisting renal disease. Studies comparing CEUS with unenhanced CT or MR show clear superiority of CEUS in both detection and diagnosis of pathology in all organs evaluated (59,60).

c) Other kidney pathology

CEUS is of great value in evaluating focal kidney masses, both cystic and solid. These masses often present as indeterminate on CT and/or MR (22). Transplanted kidneys and diseased kidneys also may also benefit from a CEUS study. Since UCAs are not nephrotoxic, they are particularly appealing for patients with compromised renal function or a single kidney (23).

d) Pregnancy

Pregnant women have limited options for managing serious medical complications that require advanced diagnostic imaging. These complications generally occur across three broad categories: malignant neoplasia, acute onset of gastrointestinal or genitourinary inflammatory conditions, and positive findings related to chronic ongoing conditions requiring routine surveillance such as inflammatory bowel disease or risk of hepatocellular carcinoma (HCC). In many instances, these complications are simply not addressed until the end of gestation.

UCAs offer a safe and effective option for managing complications during pregnancy because UCAs do not cross the placental barrier (49). CEUS has 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 (49,61).

e) Ovarian cancer

Ultrasound has been a mainstay for investigation of the pelvis in women since the introduction of endovaginal ultrasound scanning techniques decades ago. However, without UCA enhancement, ultrasound alone does not provide sufficiently detailed vascular information required to detect ovarian cancer in early stages, when treatment may be most effective.

CEUS software was added to endovaginal probes several years ago, but its use in the U.S. for ovarian cancer detection is off-label and adoption has been limited (62). Indeed, few clinicians even know that this technique is available since industry representatives cannot initiate discussion of the off-label use of this potentially life-saving imaging option.

f) Inflammatory bowel disease

CEUS, sometimes coupled with shear wave elastography, offers significant benefits for patients with inflammatory bowel disease (“IBD”). UCAs provide excellent biomarkers for bowel stricture characterization. Strictures may be inflammatory, shown to have high inflammatory activity and low stiffness, while chronic strictures requiring surgery are generally stiff with low inflammatory activity. Quantitative blood flow measurements allow for sensitive prediction of disease activity and assessment of response to therapy. The increasing incidence of IBD in pediatric and young adult

patients make the use of CEUS even more valuable, since this disease is chronic and its management requires surveillance (63,64).

g) Carotid intraplaque neovascularization

CEUS offers a unique tool for identifying vulnerable carotid plaque associated with ischemic stroke pathogenesis and risk of cardiovascular events (65). Since intraplaque neovascularization is a key indicator of plaque instability and risk of rupture, CEUS may be used to evaluate plaque surface morphology and microvascular features. Microbubble contrast agents enhance visualization of blood flow into the microvascular bed, allowing for clearer assessment of plaque microvasculature and surface characteristics, improving identification of plaque vulnerability. Unlike MR, CEUS provides real-time assessment, higher temporal resolution, wider accessibility, cost-efficiency, bedside applicability, and improved patient comfort (66). This, in turn, makes CEUS an efficient, accessible, and precise tool for early identification of vulnerable plaques in patients at risk for stroke, and for serial examinations and follow-up studies (66).

h) Lymphatic Mapping

CEUS has been used off label for mapping sentinel lymph nodes in breast cancer in thousands of patients at least since 2006, with many studies reporting no adverse reaction or minor skin irritation in extremely low numbers of patients (67). CEUS is now also used to identify lymphatic vessels for lymphaticovenous anastomosis (LVA) surgery preoperative mapping. This allows for the identification of lymphatic vessels and potential recipient veins prior to surgery in the extremities (68).

i) Additional “off label” applications

- CEUS is now an integral component of surveillance for **endovascular aortic stents** which require regular evaluation throughout their existence (18,23,45).
- CEUS has become an invaluable tool for predicting and diagnosing **pancreatic cancer,** a deadly tumor which is well visualized and confirmed with CEUS (69).
- **Gallbladder pathology** is optimally shown related to the cystic nature of the gallbladder allowing for excellent detection of both mural inflammatory and neoplastic disease (70).

5. **UCA approvals have had the effect of encouraging off-label innovation in the liver and heart, and in pediatrics**

FDA approvals of adult liver and cardiac indications, as well as pediatric indications, have created clinical comfort zones in which CEUS innovation has thrived and clinical adoption has expanded into broader liver, cardiac and pediatric uses (13,71,72). This is demonstrated by the growing number of professional guidance statements and clinical studies confirming the safety and benefits of off-label indications for CEUS of the liver and heart, as well as in pediatrics (18,19,31,34,45,46,49,57,59-65,69,70,73-78).

a) Liver imaging: The path from FDA approval to broader innovation and clinical adoption

Since 2016, when the FDA first approved a UCA to characterize focal liver lesions (FLLs), radiologists have come to appreciate that UCAs are an exceptionally safe and effective tool for assessing other liver pathology, and that CEUS assessment of the arterial, portal venous and late phases may be as accurate as CT and MR. This post-approval momentum has contributed to the development and growing adoption of new liver CEUS applications, with special significance for patients with liver tumors that are aggressive and potentially lethal if not identified early.

Numerous professional societies have now published clinical practice guidelines that formally recognize the benefits of off-label CEUS for liver cancer detection, diagnosis and management (18,45,53,79). In addition, research scientists stepped up publication of studies confirming the safety and clinical benefits of CEUS for liver imaging and recognizing the incomparable advantages for dynamic real-time diagnostic capability, with the highest spatial resolution of any imaging modality and excellent sensitivity to any recurrent tumor. In 2018, CEUS was 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. The CEUS LI-RADS Working Group also published an important paper validating CEUS for HCC (72) – the most common primary tumor of the liver, the third highest cause of mortality due to its aggressiveness, and the only solid tumor malignancy with a steadily increasing incidence in North America. The Working Group's multi-center study demonstrated specificity in excess of 95% for the CEUS LI-RADS category LR-5, allowing for HCC diagnosis and treatment without biopsy. This approach is now recognized in the guidelines of the American College of Radiology (ACR) (80), the American Association for the Study of Liver Disease (AASLD) (81,82), and the Organ Procurement and Transplantation Network (OPTN) (82).

The following are examples of the clinical significance of additional off-label CEUS liver applications that have grown in use since 2016:

- UCAs are frequently used to characterize nodules detected by routine grayscale ultrasound surveillance of patients at risk for developing HCC. While contrast-enhanced CT and MR are also options for follow up characterization, CEUS offers a reliable, real time and more cost-effective option using the same modality as used for primary surveillance (18).

- CEUS greatly improves the differentiation between HCC and intrahepatic cholangiocarcinoma (ICC), the second most common malignant liver tumor. This differentiation is critical when treatment options are chosen (46) and is a result of the contrast agent composition. While microbubble UCAs are purely intravascular, MR and CT contrast agents can pass through the vascular endothelium into the tumor interstitium (46).

- CEUS has become an important tool for reliably detecting residual or recurrent tumors and characterizing the geographic patterns of recurrence. This is especially significant because liver tumors have a high recurrence rate (18).

- CEUS is used to guide interventional radiology procedures and localize viable vascular tumor within complex tumor masses. CEUS guidance is more common for interventional liver tumor procedures and is less accepted for interventional procedures outside the liver (83) .

- CEUS also plays a vital role in guiding the performance of local ablative therapies for treating small tumors when accessible and is generally useful for guiding liver ablation where the identification of viable vascular tumor is essential (55).

- Post-therapy, CEUS may be used to compliment ultrasound for secondary surveillance. CT and MR are not suitable options because they do not offer sufficient resolution to guide interventional therapies (17) .

- Dynamic CEUS is also being used to predict 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 (39). In addition, CEUS may eliminate the need for biopsy to confirm a HCC diagnosis.

In sum, following the approval of a UCA for liver imaging, CEUS has become a success story within liver cancer circles. Approval has fostered greater awareness of the potential uses and advantages of CEUS, and that in turn has increased adoption and led to further innovation in the context of liver imaging.

b) Cardiovascular CEUS: From approvals to broader innovation and use in echocardiography

Another success story grew out of the FDA's approval of three UCAs for cardiovascular imaging, in particular for evaluation of the left ventricle and endocardial borders. As familiarity with CEUS grew in the echocardiography community, clinicians came to appreciate the high resolution, real-time CEUS images and realized that off-label CEUS scans may offer significant diagnostic value with no added risk (6,15,36). Consequently, echocardiography labs often use UCAs off-label for:

- Quantification of the heart's pumping capacity (left ventricular ejection fraction) (2,84-86).
- Assessment of blood flow under stress (stress echocardiography) (87-91).
- Evaluation of myocardial ischemia (perfusion imaging) (92,93).
- Imaging of patients with difficult imaging windows – for example, due to scarring resulting from breast cancer treatment, implants, or obesity (84,94).
- Assessment of regional wall motion abnormalities (2,87,95-97).
- Evaluation of valve function (98,99).
- Distinguishing avascular and vascular structures for individuals with intra-cardiac masses (100).
- Identification of apical hypertrophic cardiomyopathy and an associated apical aneurysm (101).
- Excluding a mural thrombus in patients with apical LV dysfunction (100).
- Inotropic and vasodilator stress testing (85,88,89,91,93,96,97,100,102-108).

The Intersocietal Accreditation Commission guidelines for accrediting adult echocardiography laboratories now require the off-label use of a UCA during stress echocardiography under certain conditions (36). New clinical practice guidelines and published protocols for echocardiography also support the off-label use of UCAs for stress echocardiography and cardiac perfusion imaging (36,100,102,103). Additionally, the American Society of Echocardiography recommends certain off-label uses of UCAs in echocardiography (102).

c) Pediatric CEUS: FDA approvals led to expanded applications for children

The impressive power of FDA approval, and its ability to stimulate confidence, innovation and adoption, are especially evident in the dramatic growth of CEUS for pediatric imaging. CEUS is an ideal pediatric imaging option because it offers a highly accurate, affordable, real-time diagnostic tool without ionizing radiation (which increases a child's lifetime risk of cancer) or the need for sedation and anesthesia. CEUS also may

be performed at the child's bedside and is more comfortable and patient-friendly than contrast-enhanced CT and MR -- which often require sedation and anesthesia, increasing cost, risk and duration or procedure, and potentially complicating workflow.

The FDA issued its first two UCA approvals for pediatric indications in 2016, following a special ICUS briefing for FDA staff and a follow-up white paper addressing the safety and benefits of CEUS for children (109). The initial pediatric approval covered CEUS for evaluation of FLL via intravenous administration. A second pediatric approval soon followed, covering assessment of known or suspected vesicoureteral reflux via intravesical application. Both pediatric approvals were granted without prospective pediatric clinical trials, based instead on published literature describing favorable safety and efficacy in children. This progress reflected the FDA's strong commitment to the welfare of pediatric patients and the agency's practical understanding of the imperative of offering children diagnostic imaging options that are safe, reliable, noninvasive and patient friendly (109).

Following the initial pediatric approvals, the growth of pediatric CEUS, including off-label indications, has been nothing short of astonishing. For example, CEUS is now being investigated for use in imaging the brain to assess tissue perfusion and cerebral pathologies including stroke, tumors, epilepsy and hypoxic–ischemic injury (110). This work is being explored not only in infants with open fontanelles but also in older children via a transtemporal window or surgically created acoustic window (110). Additional novel off-label uses involve small organs such as the thyroid gland, lymph nodes, testes, ovaries and uterus, (77) complicated pneumonia, (111) and kidney trauma, renal cortical cysts, non-Hodgkin's lymphoma with secondary liver deposits, retropharyngeal abscess, necrotizing pancreatitis, and vesicoureteral reflux (74). Today, CEUS often replaces CT to look for injury to the solid viscera within the abdomen and pelvis following minor and some major trauma presenting to the emergency department, and follow-up imaging for all levels of trauma is excellent.

As predicted by the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB), the FDA's initial pediatric approvals were "a welcome first step" toward broader acceptance of CEUS in the pediatric imaging community (112). The Society of Pediatric Radiology now fully incorporates CEUS within its educational mandate (109). ICUS offers numerous CME-accredited webinars on approved and off-label pediatric CEUS indications in partnership with the Center for Pediatric Contrast Ultrasound of the Children's Hospital of Philadelphia (CHOP), a world leader in all aspects of pediatric CEUS. In addition, CHOP offers hands-on training programs that have educated hundreds of pediatric physicians and sonographers.

The growth of pediatric CEUS in the U.S. has made our pediatric CEUS community the envy of the world. The FDA's pediatric approvals, and its commitment to the well-being of pediatric patients, must be credited for bringing this success about.

Policy Considerations

1. A whole-body indication for approved UCAs would be consistent with FDA policy favoring drug repurposing, innovation and protection of public health.

UCAs represent an ideal opportunity to repurpose approved drugs to help address unmet medical needs across a range of diseases and conditions. As the FDA announced on May 11, 2026:

> Identifying potential new uses—such as a new indication …—for FDA-approved drugs can help accelerate the availability of treatments by using existing knowledge about the drugs, including a drug's safety profile. This request for public input is part of a broader FDA initiative to update the labeling of FDA-approved drugs, when supported by sufficient evidence, to ensure that information in the labeling is clinically meaningful for health care providers and patients and scientifically up to date (113).

The agency also stated that the promise of repurposed drugs is of particular interest where, as here, "there are scientific data that could support approval of potential new uses but there appears to be limited commercial incentives to pursue approval of those uses." As detailed elsewhere in this statement, there is overwhelming scientific data supporting the safety and benefits of UCAs across approved and off-label uses. By simply moving an external ultrasound transducer, the clinician can scan multiple organs following a single injection of contrast. However, organ-by-organ regulatory approvals create costly, burdensome and illogical commercial disincentives to seeking broader indications that would expand patient access to safe, reliable, real-time and affordable advanced diagnostic imaging without exposure to ionizing radiation or iodinated dye.

Policy analysts recently published comments supporting the FDA's commitment to repurposing drugs and called for regulatory reform. Although the analysts focused on repurposing generic drugs, their conclusions are equally applicable to approved UCAs. As they note:

> The FDA could modernize the process to ensure drug labels include all evidence-backed uses, which are key to driving

> adoption. Nonprofits, academics and other nontraditional developers have generated evidence for some new uses of generic drugs but there's no clear path for them to secure label updates. The FDA could streamline routes for nonindustry developers to bring strong evidence forward and ensure drug labels include all evidence-based uses. …
>
> By rewarding results and updating regulatory pathways, we can uncover new uses for generic drugs. These long-approved, affordable medicines are on pharmacy shelves. We need the policy to unlock their full potential (114).

The FDA's interest in repurposing approved drugs builds on existing agency initiatives aimed at updating drug labeling when supported by scientific evidence. These initiatives include the Best Pharmaceuticals for Children Act, the Making Objective Drug Evidence Revisions for New (MODERN) Labeling Act of 2020, and Project Renewal. Further, repurposing approved UCAs for whole-body use would be consistent with the agency's commitment to leveraging innovation in order to improve health care, broaden access, and advance public health -- a key priority of the agency (115). It also would directly advance the FDA's core mission to protect public health.

2. For consistency and fairness, FDA approvals should be guided by precedent – including approvals of whole-body contrast CT and MR

While UCAs have been subjected to costly and burdensome organ-by-organ approval procedures, the FDA has approved CT and MR contrast agents for whole-body indications. The following chart offers examples of CT and MR contrast agents approved to enhance multiple body parts following a single injection:

Broad body approvals – Contrast CT and MR		
Conray (Mallinckrodt)	CT	Brain, liver, pancreas, kidneys, abdominal aorta, mediastinum, abdominal cavity and retroperitoneal space.
Hexabrix (Guerbet)	CT	Brain and body imaging; other
Isovue (Bracco)	CT	Head and body; other
Omnipaque (GE Healthcare)	CT	Head and body; other
Omniscan (GE Healthcare)	MR	Brain; spine; thoracic, abdominal, pelvic cavities; retroperitoneal space
Optiray (Guerbet)	CT	Head and body; other
Oxilan (Guerbet)	CT	Head and body; other

Ultravist (Bayer)	CT	Head and body; other
Visipaque (GE Healthcare)	CT	Head and body; other
Vueway (Bracco)	MR	Central nervous system and body (head and neck, thorax, abdomen, pelvis and the musculoskeletal system)

Additionally, the FDA is considering approval of two new MR agents (gadoquatrane (Bayer) and Mangaciclanol (GE Healthcare)) for body indications, and the latter has been fast-tracked.

CT and MR abdominal scans are often used to assess all visualized organs within the entire field of view following a single injection of contrast. CT and MR fields of view are not organ specific and generally include the liver, biliary tract, pancreas, both kidneys, the bowel, the spleen and the organs of the pelvis and retroperitoneum.

Whole-body approvals of CT and MR agents establish a logical precedent for guiding the approval of whole-body indications for UCAs. The result would be more consistent and fair regulation of diagnostic imaging agents, allowing clinicians to use a single injection of a systemic UCA to follow disease across organs in furtherance of the agency's ultimate commitment to protecting public health.

Conclusion

ICUS urges the FDA to repurpose approved UCAs and recognize a whole-body indication. Drug repurposing focuses on establishing new uses of FDA-approved drugs when the new uses are supported by safety and effectiveness data, taking into account existing knowledge regarding established safety profiles and the benefits and risks of the potential new uses. Favorable UCA safety profiles and clinical benefits across multiple organs are well documented. Additionally, organ-by-organ approvals are unnecessary, cost-prohibitive and clinically illogical because a single intravenous injection of a microbubble UCA will enhance images throughout the body. The choice of target does not alter risk.

The status quo may have an especially harmful impact on the care and survival of individuals who do not have access to alternative advanced imaging options. These individuals include patients with chronic kidney disease or acute kidney injury who are not candidates for contrast-CT or MR due to the increased risk of nephrotoxicity; pregnant patients who wish to avoid other contrast media and exposure to ionizing radiation; patients who cannot easily be moved to a CT or MR imaging suite; obese patients; individuals with fatty liver disease; and breast cancer patients with

compromised imaging windows. Additionally, patients in rural hospitals may not have access to on-site CT or MR due to the high cost of installation, maintenance and operation. And, as insurance deductibles increase across geographical regions, many patients simply cannot afford a contrast-CT or MR scan. For all of these patients, FDA-approval of whole-body CEUS would align with the agency's mission of protecting public health by expanding access to a potentially life-saving, affordable and accurate diagnostic imaging option.

We sincerely appreciate your attention to the information provided in this Statement. Please let us know if we can provide any additional input.

Respectfully submitted,

The Board of Directors of the International Contrast Ultrasound Society 2.0

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