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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 approval of a whole-body indication
for 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 streamlined consideration and approval of a whole-body indication for UCAs ².

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

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

² Petitioner has submitted a separate Citizen Petition to support removal of boxed warnings from product labels of 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 the safety and clinical benefits of repurposing approved imaging drugs in addition to therapeutic drugs.

accuracy, disease management and patient outcomes. ICUS members include healthcare professionals, scientists and patients.

CEUS is a safe, patient-friendly, 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 [1-27].

At present, UCAs are only approved for certain adult liver and cardiac indications, and for certain pediatric indications [28-30]. These limited applications do not represent the full potential of UCAs, which are capable of safely and effectively assessing and managing pathology occurring throughout the body (including the kidney, breast, thyroid, pancreas, spleen, bowel, musculoskeletal system, testicles, uterus and ovaries); detecting organ injury following acute trauma; guiding interventional procedures; and monitoring therapy [14, 27, 31-34].

A. Actions Requested

ICUS respectfully requests that the FDA:

1. Approve a whole-body indication for UCAs, eliminating the need for organ-by-organ submissions.
2. Expedited review of this indication, recognizing the significant unmet clinical needs addressed by UCAs -- especially for patients with no other option for advanced imaging.
3. Accept real-world data and evidence in support of safety and efficacy for whole-body use [35, 36].

The current organ-specific approval process is clinically illogical because a single UCA injection enhances images of organs throughout the body. Enhancement patterns are not organ-specific, and there is no evidence or logical basis for believing that the choice of organ alters risk. The excessive costs, burdens and inefficiencies associated with organ-by-organ approvals have the effect of discouraging sponsor applications for broader approvals, restricting physician access to training opportunities, depressing CEUS adoption outside the heart and liver, and limiting patient access to a safe, affordable health care option.

B. Statement of Grounds

This Statement of Grounds will present the factual and legal grounds on which this Petition relies:

1. UCAs are systemic agents with enhancement patterns that are not organ-specific.
2. UCAs are safe.
3. UCAs are efficacious across a broad range of indications.
4. Limited UCA approvals may confuse clinicians and patients, limit CEUS education, and discourage off-label uses that are safe and beneficial.
5. Clinical benefits outside the liver and heart are now widely recognized. Examples include:
 - a. Renal imaging.
 - b. Carotid intraplaque neovascularization.
 - c. Pregnancy.
 - d. Ovarian cancer.
 - e. Lymphatic mapping.
 - f. Breast cancer.
 - g. Inflammatory bowel disease.
 - h. Incidental detection of pathology near the liver.
 - i. Examples of additional off-label applications.
6. UCA approvals have encouraged innovation for liver, heart and pediatric imaging.
7. Policy considerations favor a whole-body approval.
 - a. FDA precedent: Body approvals of CT and MR contrast agents.
 - b. Approval of a whole-body indication for approved UCAs would align with FDA policies favoring drug repurposing, innovation and protection of public health.

8. Conclusion.

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

UCAs are 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, they circulate unimpeded throughout the patient's microcirculation and enhance ultrasound images of organs **throughout the body**. After several minutes, the 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. Bioeffects are minimal since a very low mechanical index (MI) is used [8, 37, 38].

During a CEUS examination, the clinician can obtain a broad understanding of pathology across organs simply by moving an external transducer to follow disease. For example, a radiologist using CEUS to examine the liver may spot a suspicious lesion in the kidney or bowel; moving the transducer allows for immediate assessment of neighboring organs without referring the patient for additional downstream tests. However, doing so is not yet FDA-approved.

2. UCAs are safe.

UCAs are among the safest contrast media available. Clinical trial data along with a growing and compelling body of investigator-initiated studies clearly demonstrate that UCAs have an excellent safety profile across a variety of clinical settings, and serious adverse events are rare [4, 8, 11, 12, 20, 23, 24, 39, 40]. The risk of acute hypersensitivity reactions, including complement activation-related pseudo-allergy (CARPA), is approximately 1 in 10,000 administrations [14, 41-43]. In a large study of 23,188 abdominal CEUS examinations, serious adverse events occurred in 0.0086% of examinations (8.6 per 100,000), with no fatal events [3]. More recent pooled data from more than 1 million adults and 36,000 children reported severe acute adverse drug reactions at approximately 6 per 100,000 administrations in adults and 16 per 100,000 administrations in children [5]. Although rare fatal reactions have been reported, standard emergency management was effective in nearly all serious reactions [5], and published multisocietal consensus guidelines on safe administration now promote standardized laboratory practice to mitigate these risks [8]. Rare CARPA reactions also occur with other drugs or agents [8, 10, 11, 23, 44-47]. Mitigation of rare risk may be feasible through dilution, slow administration, and screening [44, 45].

UCAs compare favorably in safety with contrast agents used to enhance CT or MR scans [5, 8]. UCAs do not contain iodinated dye, which is present in CT contrast agents and is associated with a risk of nephrotoxicity. In addition, UCAs do not contain gadolinium, which is present in MR contrast agents and is associated with a risk of nephrogenic

systemic fibrosis in individuals with advanced renal dysfunction and, in some cases, gadolinium deposits in the brain (the long-term consequences of which are unknown).³ Additionally, CEUS does not expose patients or staff to ionizing radiation, which increases a patient's cumulative lifetime risk of cancer.

3. UCAs are efficacious across a broad range of indications.

The benefits of UCAs are well established across a range of indications, and the clinical, scientific and health care policy ecosystems are now in alignment in recognizing the value of broader UCA uses. Clinical practice guidelines promulgated by national and international professional societies reflect a strong consensus in favor of UCA use across multiple organ systems [14, 19, 48, 49]. Indeed, off-label UCA 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 [49, 50]. A recent consensus statement by 12 ultrasound professional societies also recognizes broader CEUS use [8]. In addition, Medicare reimburses non-cardiac CEUS under CPT codes that are not organ-specific, and effective January 1, 2026, the Centers for Medicare & Medicaid Services (CMS) reassigned non-cardiac CEUS to the same hospital outpatient payment level as contrast-enhanced CT and MR (APC 5572), approximately doubling hospital outpatient payment [51]. The National Education Curriculum for diagnostic medical sonography has also been updated to expand CEUS training in general and cardiac sonography [52], and the Commission on Accreditation of Allied Health Education Programs (CAAHEP) has adopted accreditation standards requiring accredited sonography programs to teach CEUS principles, safety, administration and clinical applications [53].

CEUS benefits are based in part on image quality and diagnostic versatility. Studies also show that CEUS sensitivity and specificity are often equivalent to, and sometimes are superior to, contrast-enhanced CT and MR [16]. By adding a UCA to a standard ultrasound liver imaging protocol, interpreter accuracy may improve from 35–42% with gray-scale sonography alone to as much as 88% with CEUS [54, 55]. In a separate series of 452 focal liver lesions that were indeterminate on baseline sonography, accuracy similarly increased from 49–51% with gray-scale imaging to 85–88% with CEUS [56]. 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 [57]. CEUS also improves detection of residual or recurrent tumor after treatment and offers an important option for perfusion assessment [13].

³ The availability of gadolinium, a rare-earth element, is largely dependent on mining and processing in China.

Further, by providing a reliable diagnosis up front, in real time, UCAs can reduce the need for downstream tests and procedures, improve disease management and outcomes, lower healthcare costs, reduce length of stay, improve health care efficiencies and streamline workflows [1, 2, 24, 25]. CEUS also avoids the long waits for CT and MR at many institutions, so diagnosis and treatment initiation may be speedier and more efficient. Additionally, small, portable, 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 gantry required to house CT and MR scanners. Since ultrasound systems are more readily available than CT and MR [58], 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.

4. Limited UCA approvals may confuse clinicians and patients, limit CEUS education, and discourage off-label uses that are safe and beneficial.

While off-label use of approved drugs may be common it is not without significant real-world limitations [59]. 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 [60]. Speakers at CME-accredited educational programs sponsored by industry have been instructed not to discuss off-label uses, insisting that these professional experts withhold comment on 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 administrators are reluctant to perform off-label CEUS studies even when doing so is

evidence-based, professionally recommended, legal and reimbursed. These health care professionals may perceive increased clinical risk and legal exposure for novel unapproved CEUS uses even though the examinations would be performed with the same UCA and ultrasound system used “on label” for other studies. Administrators also may require defensive production of exhaustive information to patients along with informed consent [59]. To avoid these perceived risks and burdens, 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 diagnosis [61].

5. Clinical benefits outside the liver and heart are now widely recognized.

Several examples will illustrate the pressing need for and beneficial uses of CEUS applications throughout the body.

a. Renal imaging.

UCAs offer an important contrast option for assessing solid organ perfusion in patients with chronic kidney disease, which affects an estimated 15% of U.S. adults [62], without any known risk of nephrotoxicity as may occur with iodinated contrast or nephrogenic systemic fibrosis as may occur with gadolinium-based agents [63, 64]. Because UCAs are not cleared by the kidneys, CEUS requires no renal function screening, prophylaxis, or dose adjustment. Unenhanced CT or MR scans 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.

Similarly, UCAs, which are not nephrotoxic, can be used in patients with renal compromise or a single kidney without renal precautions [19, 49]. Peer-reviewed studies show that CEUS produces excellent assessments of organ perfusion without risk of nephrotoxicity or kidney damage, regardless of the degree of preexisting renal disease [3, 65, 66]. In a prospective study of patients unable to receive CT contrast, most with renal failure, CEUS was superior to unenhanced CT for characterizing focal liver and kidney pathology, achieving 100% characterization in both organs [67].

CEUS also is of great value in evaluating focal kidney masses, both cystic and solid [18, 68]. These masses often present as indeterminate on CT and/or MR. Transplanted kidneys and diseased kidneys also may benefit from a CEUS study.

b. Carotid intraplaque neovascularization.

CEUS offers a unique tool for identifying vulnerable carotid plaque associated with ischemic stroke pathogenesis and risk of cardiovascular events [69, 70]. 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 [71]. This 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 [71].

c. 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 may offer a safe and effective option for managing complications during pregnancy because UCAs do not appear to cross the placental barrier [72]. CEUS has been performed safely during pregnancy with excellent results, including the detection and characterization of primary and secondary malignant tumors, in some cases avoiding the need for CT or MR [72, 73].

d. Ovarian cancer.

Ultrasound has been a mainstay for investigation of the pelvis in women since the introduction of endovaginal ultrasound 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. Yet clinicians are not always aware that CEUS is a potential option in part because industry representatives cannot initiate discussion of the off-label use of this potentially life-saving modality [49, 74].

e. Lymphatic mapping.

CEUS has been used off-label for mapping sentinel lymph nodes in thousands of breast cancer patients at least since 2006, with many studies reporting no adverse reaction or minor skin irritation in extremely low numbers of patients [75]. 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 [76].

f. Breast cancer.

Contrast-enhanced echocardiography may be useful for cardiac imaging in breast cancer patients whose acoustic windows have been degraded by mastectomy, reconstruction, or chest-wall radiation [77].

g. 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 [78, 79].

h. 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.

i. Examples of additional off-label applications.

- CEUS is now an integral component of surveillance for **endovascular aortic stents** which require regular evaluation throughout their existence [49].

- CEUS has become an invaluable tool for predicting and diagnosing **pancreatic cancer**, a deadly tumor which is well visualized and confirmed with CEUS [80].
- **Gallbladder pathology** is optimally shown related to the cystic nature of the gallbladder allowing for excellent detection of both mural inflammatory and neoplastic disease [81].
- CEUS is a useful imaging option for critically ill patients and others who cannot easily be moved to a CT or MR imaging suite [82, 83].
- Patients with high BMI or fatty liver may benefit from CEUS lesion detection and characterization due to advances in ultrasound technology and transducer design [84, 85].

The benefits of CEUS may be most compelling for patients who are not candidates for contrast-CT or MR, and for those without access to these modalities for cost and geographical reasons. As insurance deductibles increase, many patients simply cannot afford CT and MR imaging [86]. For these individuals, CEUS may be the only safe, reliable and accessible imaging option available

6. UCA approvals have encouraged innovation for liver, heart and pediatric imaging.

It is the considered opinion of the undersigned that 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 [9, 87, 88]. Petitioner believes 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 outside of currently-approved indications in the liver and heart, as well as in pediatrics [14, 15, 18, 27, 33, 49, 57, 61, 67, 69, 70, 72-74, 78-81, 89-94].

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 [14, 48, 49]. In addition, research scientists have stepped up publication of studies confirming the safety and clinical benefits of CEUS for liver imaging and recognizing the distinctive advantages for dynamic real-time diagnostic capability, including the highest temporal resolution of any contrast-enhanced imaging modality, high spatial resolution, and excellent sensitivity to recurrent tumor. In 2016, the American College of Radiology (ACR) released CEUS LI-RADS [95], extending the Liver Imaging Reporting and Data System, which is now widely used for liver imaging in North America and beyond, to CEUS. The CEUS LI-RADS Working Group also published an important paper validating CEUS for HCC – a common and aggressive primary tumor of the liver [88]. The Working Group's multi-center study demonstrated specificity of 95.1% with a positive predictive value of 97.3% 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) [96], the American Association for the Study of Liver Disease (AASLD) [97], and the Organ Procurement and Transplantation Network (OPTN) [98].

The following examples demonstrate the growing clinical significance of off-label CEUS liver applications 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 [14].
- 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 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 [57].
- 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 [14].

- CEUS is used to guide interventional radiology procedures and localize viable vascular tumor within complex tumor masses.
- 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 [13].
- Post-therapy, CEUS may complement conventional ultrasound for surveillance of treatment response. During and after interventional therapy, CEUS offers real-time visualization of tumor vascularity and viable tumor tissue, supporting treatment guidance and immediate assessment of treatment response without ionizing radiation, with the added advantage of bedside availability [13].
- 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 [55]. 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 of a liver indication 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 cardiac applications. 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 [2, 11]. Consequently, echocardiography labs now use UCAs more broadly for:

- Quantification of the heart's pumping capacity (left ventricular ejection fraction) [99-102].
- Assessment of blood flow under stress (stress echocardiography) [103-107].
- Evaluation of myocardial ischemia (perfusion imaging) [108, 109].
- Imaging of patients with difficult imaging windows – for example, due to scarring resulting from breast cancer treatment, implants, or obesity [84, 100].
- Assessment of regional wall motion abnormalities [99, 102, 104, 110, 111].

- Evaluation of valve function [112, 113].
- Distinguishing avascular and vascular structures for individuals with intra-cardiac masses [114].
- Identification of apical hypertrophic cardiomyopathy and an associated apical aneurysm [115].
- Excluding a mural thrombus in patients with apical LV dysfunction [114].
- Inotropic and vasodilator stress testing [43, 101, 103, 106, 107, 109-111, 114, 116-121].

Recent clinical practice guidelines and published protocols for echocardiography also support the use of UCAs off-label for stress echocardiography and cardiac perfusion imaging [43, 114, 116]. Additionally, the American Society of Echocardiography recommends certain off-label uses of UCAs in echocardiography [116].

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 [92, 122-141]. 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 cumulative, lifetime risk of cancer). 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 of 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 [9]. 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 safe, reliable and more comfortable diagnostic imaging options [123].

Petitioner believes that, 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 [132]. 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 [132]. Additional novel off-label uses involve small organs such as the thyroid gland, lymph nodes, testes, ovaries and uterus [92], complicated pneumonia [135], and kidney trauma, renal cortical cysts, non-Hodgkin's lymphoma with secondary liver deposits, retropharyngeal abscess, necrotizing pancreatitis, and vesicoureteral reflux [90, 126, 127, 129, 134, 137]. Today, CEUS can complement CT in the evaluation of abdominal and pelvic trauma, and in selected patients it may provide an alternative to CT for the detection and follow-up of solid-organ injuries, particularly during serial follow-up examinations.

As noted 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 [94]. CEUS is now a regular part of pediatric radiology education, including a dedicated compendium in Pediatric Radiology [122]. 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 the U.S. pediatric CEUS community an international leader in the field. The FDA's initial pediatric approvals, and its commitment to the well-being of our young patients, must be credited for bringing this success about.

7. Policy considerations favor a whole-body approval.

a. FDA precedent: Body approvals of CT and MR contrast agents.

While UCAs are subjected to costly and burdensome organ-specific approval procedures, various CT and MR contrast agents have been approved for multi-organ and body indications. This allows use of CT and MR abdominal scans to assess all visualized organs within the entire field of view following a single injection of contrast.

The following chart identifies examples of CT and MR contrast agent approvals for multiple body parts following a single injection:

Body approvals – CT and MR contrast agents		
Ambelvist (Bayer)	MR	Central nervous system and body (head and neck, thorax, abdomen, pelvis and the musculoskeletal system) ⁴
Conray (Guerbet; Liebel-Flarsheim)	CT	Brain, liver, pancreas, kidneys, abdominal aorta, mediastinum, abdominal cavity and retroperitoneal space.
Isovue (Bracco Diagnostics)	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; Liebel-Flarsheim)	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)

Source: current FDA-approved prescribing information for each product [142].

Additionally, an investigational MR contrast agent (mangaciclano; GE Healthcare) has received Fast Track designation for CNS and body imaging and is in Phase 2/3 clinical trials [143]. Other body approvals have been granted but are not listed above because they are no longer marketed (e.g., Hexabrix and Oxilan, both of which were CT agents).

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.

b. Approval of a whole-body indication for approved UCAs would align with FDA policies favoring drug repurposing, innovation and protection of public health.

The FDA is seeking opportunities to repurpose approved drugs for broader uses [144]. Although significant attention has been paid to the repurposing of *therapeutic drugs*, Petitioner believes that UCA *imaging drugs* offer an ideal opportunity to leverage existing safety data in order to extend applications and help address unmet medical needs across a wider range of diseases and conditions. Scientific support for whole-body applications

⁴ Newly approved in June 2026. Like other gadolinium-based agents, Ambelvist carries boxed warnings.

is compelling, and the safety profile, dosage and route of administration will be the same. Accordingly, the FDA's stated criteria for repurposing approved drugs would be met by repurposing UCAs for whole-body use.

The FDA's goals, announced on May 11, 2026, also point to repurposing of UCAs:

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 [145].

The announcement 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.”

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 [146].

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 [147]. It also would directly advance the FDA's core mission to protect public health.

8. Conclusion

Limited, organ-by-organ approvals of UCAs do not reflect the full potential of these versatile, systemic agents to safely detect and monitor disease in real time throughout the body while reducing unnecessary downstream tests, lowering overall costs and avoiding ionizing radiation. Further, the excessive costs, burdens and inefficiencies associated with organ-specific approvals have the practical effect of discouraging sponsor applications for broader approvals and restricting clinician access to training opportunities on clinically important but unapproved uses that are recommended in national and international guidelines and impact health care.

Whole-body approvals would leverage a compelling body of existing safety data, guidelines and clinical experience. They would align with the FDA's precedents for approval of CT and MR contrast agents for body indications and approval of pediatric UCA indications based on published literature, pooled analyses, society guidelines and real-world data [9]. And, they would support FDA initiatives for drug repurposing, innovation, and improving the public's health care options.

Petitioner, therefore, respectfully requests the FDA grant this Petition by affirming that the existing evidence is sufficient to support a whole-body indication for approved UCAs. Petitioners also recommend expedited review of supplemental new drug applications and approval on the basis of existing literature, pooled analyses, clinical guidelines and real-world data and evidence. While Petitioner believes existing data provide a compelling basis for such approvals, if and to the extent additional evidence may be desirable Petitioner respectfully requests acceptance of a single clinical study in lieu of organ-by-organ trials and submissions. Finally, Petitioner asks the agency to approve a whole-body indication as a means of repurposing approved imaging drugs consistent with the agency's "Drug Repurposing for Unmet Medical Needs: Request for Information" (Docket No. FDA-2026-N-4492), since (1) there is compelling scientific evidence to support effectiveness, (2) the dosage and route of administration for the new use are the same as for the approved indication, and (3) there is a comparable safety profile for the patient populations for the new use and approved indications.

Whole-body approvals would be consistent with FDA policy and precedent, and would more efficiently bring a safe and affordable healthcare option to the patients who need it. The stakes are particularly high for patients without access to alternative options for advanced imaging – and for a health care system in search of opportunities to reduce costs while improving care.

C. Environmental Impact

Pursuant to 21 C.F.R. § 25.30(h), § 25.31(a) and/or § 25.31(b), the requested action falls within the categorical exclusion for environmental impact statements.

D. Economic Impact

Petitioner does not believe that the requested action will increase the cost or price of UCAs to industry, government, or consumers; nor does Petitioner believe the requested action will impact (a) productivity of wage earners, businesses, or government; (b) competition; (c) supplies of important materials, products or services; (d) employment; or (e) energy supply or demand.

E. Certification

The undersigned certify, that, to the best of their knowledge and belief this Petition includes all information and views on which the Petition relies, and that it includes representative data and information known to Petitioner which are unfavorable to the Petition.

[Signature page follows]

Respectfully submitted,

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