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CONTRAST-ENHANCED ULTRASOUND (CEUS) IN CHILDREN

Pediatric contrast-enhanced ultrasound: shedding light on the pursuit of approval in the United States

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Abstract

For two decades, pediatric contrast US has been well accepted throughout Europe and other parts of the world outside the United States because of its high diagnostic efficacy and extremely favorable safety profile. This includes intravenous (IV) administration, contrast-enhanced US (CEUS) and the intravesical application, contrast-enhanced voiding urosonography (ceVUS). However, the breakthrough for pediatric contrast US in the United States did not come until 2016, when the U.S. Food and Drug Administration (FDA) approved the first pediatric indication for a US contrast agent. This initial approval covered the use of Lumason (Bracco Diagnostics, Monroe Township, NJ) for the evaluation of focal liver lesions via IV administration in children. A second pediatric indication followed shortly thereafter, when the FDA extended the use of Lumason for assessing known or suspected vesicoureteral reflux via intravesical application in children. Both initial pediatric approvals were granted without prospective pediatric clinical trials, based instead on published literature describing favorable safety and efficacy in children. Three years later, in 2019, the FDA approved Lumason for pediatric echocardiography following a clinical trial involving a total of 12 subjects at 2 sites. The story of how we achieved these FDA approvals spans more than a decade and involves the extraordinary dedication of two professional societies, namely the International Contrast Ultrasound Society (ICUS) and the Society for Pediatric Radiology (SPR). Credit also must be given to the FDA staff for their commitment to the welfare of children and their openness to compelling evidence that contrast US is a safe, reliable, radiation-free imaging option for our pediatric patients. Understanding the history of this approval process will impact the practical application of US contrast agents, particularly when expanding off-label indications in the pediatric population. This article describes the background of the FDA's approval of pediatric contrast US applications to better illuminate the potential pathways to approvals of future indications.

Keywords Children · Drug approval · International Contrast Ultrasound Society · Legislation · Lumason · Society for Pediatric Radiology · Ultrasound · Ultrasound contrast agent · United States Food and Drug Administration

Introduction

The key advocacy for pediatric approval of ultrasound contrast agents (UCAs) was initiated and led by the International Contrast Ultrasound Society (ICUS) in collaboration with the Contrast-Enhanced Ultrasound (CEUS) Task Force of the Society for Pediatric Radiology (SPR). Three pediatric approvals have been granted by the United States Food and Drug Administration (FDA) for use in evaluating focal liver lesions and vesicoureteral reflux and in echocardiography.

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The FDA website describes the background, reasoning and process for each of the pediatric approvals. It is important to note that the approvals are not only based on dedicated prospective studies in children that specifically target the approval process, but also on retrospective reviews of existing scientific data for an indication. This reliance on publications in the FDA approval process for pediatric contrast US is instructive for pediatric radiologists and other pediatric subspecialists performing CEUS, particularly considering current expanding off-label applications. Optimizing the existing body of CEUS research is critical in pursuit of further approvals.

In 1993, the first UCA consisting of sonicated albumin (Albunex; Molecular Biosystems, San Diego, CA) was approved for cardiac imaging in the United States [1]. Its utility for contrast-enhanced voiding urosonography (ceVUS) in children was reported in 1998, though it was later withdrawn from the market [2]. A turn for the better in pediatric CEUS came in the mid-'90s when a UCA with stabilized microbubbles became available for ceVUS [3]. Despite its off-label status, the stabilized UCA was instrumental in facilitating the widespread application of pediatric ceVUS in Europe over the next two decades.

In the United States, the perflutren protein type-A microsphere UCA, Optison (GE Healthcare, Chicago, IL), was approved by the FDA in 1997, followed by the perflutren lipid microsphere UCA, Definity (Lantheus Medical Imaging Inc., North Billerica, MA), in 2001, both for adult echocardiography (Table 1). The first approval of the sulfur hexafluoride lipid-A microspheres UCA, Lumason (Bracco Diagnostics Inc., Monroe Township, NJ), in 2014 was for the same indication in adults. This UCA, known as SonoVue outside the United States, had been approved 13 years earlier in Europe, in 2001. But in the United States, the breakthrough for pediatric contrast US came in 2016 with the FDA approval of intravenous (IV) Lumason for liver examination in children. This and subsequent pediatric approvals of Lumason have markedly accelerated the use of contrast US in children in the United States.

How did we get there? How was the FDA approval process for pediatric indications navigated? Here, we shed some light on these and related questions (Fig. 1). Not only is this of historical interest but, more important, understanding the background of the approval process will impact practical application of UCAs, particularly with expanding off-label indications in the pediatric population.

International Contrast Ultrasound Society (ICUS) and pediatric contrast-enhanced ultrasound

The ICUS was the crucial advocate for FDA approval of pediatric UCA indications based on existing scientific literature rather than dedicated prospective pediatric clinical trials. The ICUS is a grass-roots CEUS-focused organization formed by cardiologists, radiologists and other US professionals. The ICUS offers CEUS education and advocates for the safe and appropriate use of UCAs to improve patient outcomes and experiences. The organization is led by two co-presidents, a cardiologist (Steven B. Feinstein, MD) and a radiologist (Stephanie R. Wilson, MD, FRCPC), along with a board of directors comprising key CEUS thought leaders from around the world. ICUS initiatives are also supported, in part, on a pro bono basis by Dentons (San Diego, CA), an international law firm that has played a key role in helping ICUS develop a longstanding constructive relationship with the FDA and in organizing the advocacy activities of the ICUS with the FDA. This undertaking was led by two Dentons attorneys, Linda M. Feinstein, JD, and Mark W. Weller, JD.

In 2011, the FDA requested the assistance of the ICUS to investigate pediatric indications for CEUS. Several factors

Table 1 Ultrasound contrast agents approved by the United States Food and Drug Administration (FDA)

Date of first approval	Trade name and composition	Indications	Age group
12/01/1997	Optison (GE Healthcare), perflutren protein-type A microspheres	Suboptimal echocardiograms, to opacify left ventricle and improve left ventricular endocardial borders delineation	Adults
07/31/2001	Definity (Lantheus Medical Imaging), perflutren lipid microspheres	Suboptimal echocardiograms, to opacify left ventricle and improve left ventricular endocardial borders delineation	Adults
10/10/2014	Lumason (Bracco Diagnostics Inc.), sulfur hexafluoride lipid-A microspheres	Suboptimal echocardiograms, to opacify left ventricle and improve left ventricular endocardial borders delineation	Adults
03/31/2016	Lumason	US liver to characterize focal liver lesions	Adults, pediatrics
12/22/2016	Lumason	US urinary tract, to evaluate suspected/known vesicoureteral reflux	Pediatrics
11/13/2019	Lumason	Suboptimal echocardiograms, to opacify left ventricle and improve left ventricular endocardial borders delineation	Pediatrics
12/22/2016	All contrast agents	Removal of the cardiac shunt contraindication	

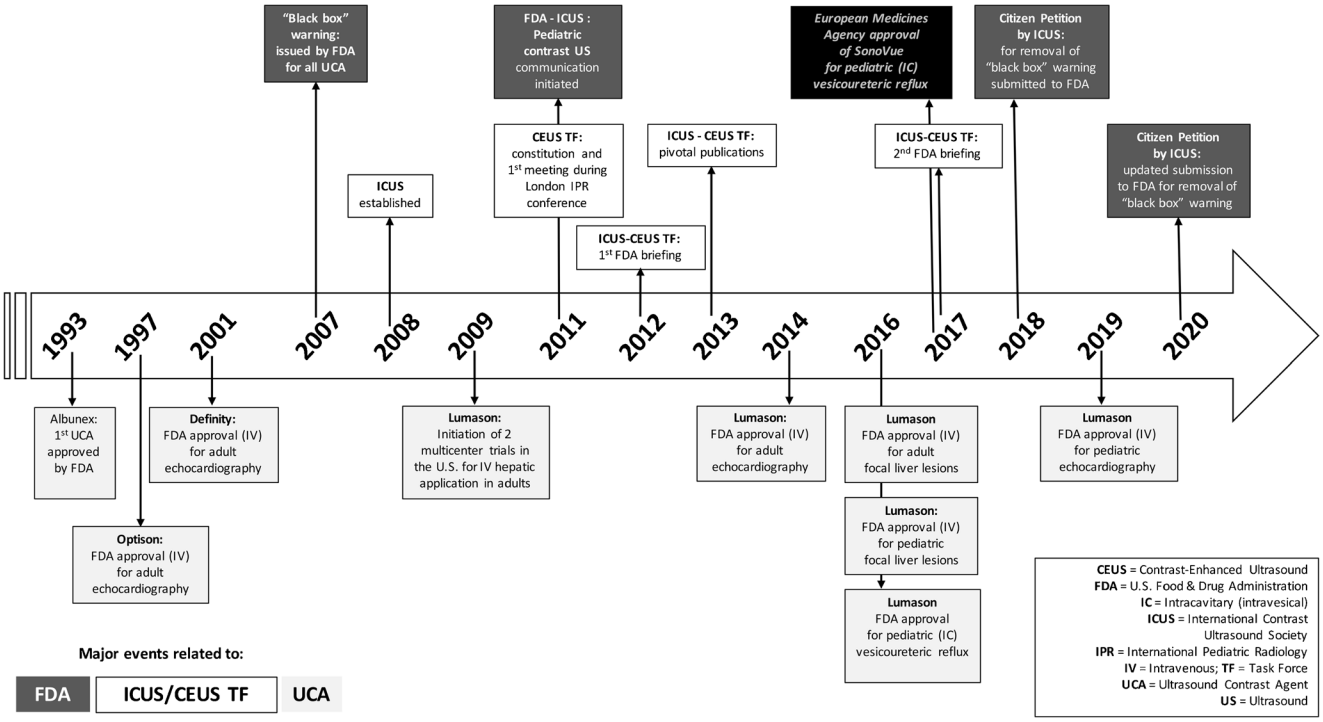

Fig. 1 Timeline for pediatric contrast-enhanced US approval and related events

might have played a role in the heightened pediatric interest expressed by the FDA, described in the following subsections.

(1) Ongoing applications of Lumason for adult indications

Bracco, a UCA manufacturer, was in the process of applying for approval by the FDA of its UCA Lumason for use in adult echocardiography. In addition, following an FDA request, in 2009 Bracco began a multicenter contrast US study in the United States for hepatic indications in adults, titled "SonoVue-enhanced US versus unenhanced US for focal liver lesion characterization" [4].

(2) Radiation reduction focus

Parallel with the aforementioned study [4] aimed at approval of SonoVue for adults, the FDA adopted a more vigorous approach to supporting the ongoing efforts of radiation exposure reduction or elimination in children [5]. This effort is reflected in the following statement from the American College of Radiology (ACR) in February 2011, titled "ACR statement on FDA radiation reduction program":

> The American College of Radiology (ACR) supports and is actively pursuing the goals of reducing any unnecessary radiation exposure that patients might receive from medical imaging exams and ensuring that patients receive appropriate imaging care. The ACR thanks the U.S. Food and Drug Administration (FDA) for recognizing the need for such efforts and supporting efforts to make sure that these issues are properly addressed [6].

(3) Legislation for pediatric drug approvals

Heightened enforcement of two existing pieces of legislation also prompted the FDA's pediatric approvals. These were enacted to expand the study of drugs in children and thereby begin to correct a serious deficit in the data on drug safety and efficacy for young patients. Ultimately, they would be used to expand information for clinicians who prescribe drugs to children and, consequently, to improve pediatric clinical care and child health outcomes. The two pieces of legislation were the Best Pharmaceuticals for Children Act (BPCA), and the Pediatric Research Equity Act (PREA), in 2002 and 2003, respectively. The Best Pharmaceuticals for Children Act offered marketplace incentives for the completion of pediatric drug studies [7]. The Pediatric Research Equity Act set the requirement for such studies in specific situations [8].

The impact of these laws for pediatric drug approvals by the FDA was reported by the Institute of Medicine [9]. In their 2014 approval letter of Lumason for echocardiographic indications in adults, the FDA added the following "required pediatric assessments":

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable. We are waiving the pediatric study requirement for ages birth to less than 9 years because necessary studies are impossible or highly impracticable. This is because the number of pediatric patients younger than 9 years of age with poor non-contrast echocardiography is small. We are deferring submission of your pediatric study for ages 9 to 17 years for this application because this product is ready for approval for use in adults and the pediatric study has not been completed. Your deferred pediatric study required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) is a required postmarketing study [10].

(4) Multicenter pediatric study

At this time, Bracco went on to conduct a multicenter study of safety and efficacy in pediatric patients ages 9–17 years, incorporating the comparison of the efficacy of Lumason contrast echocardiography with that of non-contrast echocardiography for left ventricular delineation [11]. Following a strict timeline set by the FDA, Bracco completed the postmarketing pediatric study and submitted a supplement to the approved new drug application (NDA). Accordingly, Lumason gained approval for pediatric echocardiography in November 2019.

(5) Constitution of the Society for Pediatric Radiology Contrast-Enhanced Ultrasound Task Force

Also in 2011, the same year the FDA enlisted the ICUS, several pediatric radiologists in the United States with experience or interest in contrast-enhanced US (CEUS) research or clinical off-label applications started discussions to advance pediatric contrast US in the United States. Fortunately, in 2011 the chair of the SPR Board of Directors, Dorothy I. Bulas, MD, urged the establishment of a CEUS task force [12]. This task force was constituted under the leadership of its first chairman, Frank M. Volberg, MD (Georgetown University Medical Center), and conducted its first meeting during the Joint Societies of Paediatric Radiology 6th Congress and Exhibition (IPR) in May 2011 in London, UK. The task force set out with six objectives, as outlined in Table 2. On the invitation of the ICUS in 2012, CEUS Task Force member Kassa Darge, MD, PhD (Children's Hospital of Philadelphia) was appointed as the pediatric director of the board of the ICUS. This further strengthened the collaboration between the SPR CEUS Task Force and the ICUS in advocacy for pediatric CEUS.

(6) United States Food and Drug Administration briefing

The pivotal meeting with the FDA was conducted April 25, 2012, where the SPR and ICUS jointly briefed the FDA on the safety and benefits of pediatric contrast US. Four members of the CEUS Task Force made the following presentations:

1) "Promoting pediatric contrast-enhanced US in the USA: joint efforts by SPR and ICUS," Frank M. Volberg, MD;
2) "Intravesical contrast-enhanced US in children for the diagnosis of vesicoureteric reflux: a widespread indication for US contrast in children — current safety and diagnostic efficacy data" and "Potential improvements in diagnostic imaging safety in children with the use of contrast-enhanced US," Kassa Darge, MD, PhD;
3) "Intravenous contrast-enhanced US in children: current applications and safety data," M. Beth McCarville, MD (St. Jude Children's Research Hospital); and
4) "Lessons from the lab: future US contrast-enhanced applications in children," Harriet J. Paltiel, MD (Boston Children's Hospital).

In addition, from the ICUS side, the co-president Steven B. Feinstein, MD, described the lack of evidence regarding the contraindication of UCA in children with known or suspected cardiac shunts. These presentations generated constructive discussion with the FDA participants. We were able to draw a few lessons from this meeting that would serve to further facilitate the approval of UCAs for pediatric indications. These included the following: (1) the need to publish an up-to-date review article on the safety of UCAs in children; (2) the importance of assembling a comprehensive article detailing the reasons for the need to remove the cardiac shunt contraindication for UCA administration; (3) the realization that as professional societies we were not in a position to apply for pediatric approval but that the request for approval could only be made by each UCA manufacturer separately; (4) the understanding that approval for IV use in children would require additional data because those existing at the time appeared not to be adequate; (5) published data could be used for the purpose of NDA application; and (6) regarding ceVUS, the availability of abundant publications on diagnostic efficacy and safety would allow the manufacturer to apply for approval without the need for additional prospective studies.

Table 2 Objectives of the Contrast-Enhanced Ultrasound (CEUS) Task Force of the Society for Pediatric Radiology (SPR)

Number	Objective
1	Help promote CEUS as a useful, low-cost, radiation-free imaging modality in pediatric imaging
2	Develop relationships with manufacturers, regulators, media, other imaging organizations and appropriate advocacy groups
3	Explore ways of developing CEUS as a useful, practical imaging tool, including clinical trials and off-label uses
4	Encourage scientific research involving CEUS
5	Help educate SPR members, pediatricians and parents about the benefits of CEUS in pediatric imaging
6	Help coordinate/support multicenter clinical trials involving CEUS

(7) Pivotal pediatric contrast-enhanced ultrasound publications

After the FDA briefing, the SPR CEUS Task Force and the ICUS went on to work on two important documents, publishing them in July 2013: "Safety of contrast-enhanced US in children for non-cardiac applications" [13] and "Safety of ultrasound contrast agents in patients with known or suspected cardiac shunts" [14]. On the topic of UCA safety, the summary of the review stated the following:

> The five published studies using pediatric intravenous contrast-enhanced US comprise 110 children. There is no mention of adverse events in these studies. From a European survey 948 children can be added. In that survey six minor adverse events were reported in five children. The intravesical administration of US contrast agents for diagnosis of vesicoureteric reflux entails the use of a bladder catheter. Fifteen studies encompassing 2,951 children have evaluated the safety of intravesical US contrast agents in children. A European survey adds 4,131 children to this group. No adverse events could be attributed to the contrast agent. They were most likely related to the bladder catheterization. The existing data on US contrast agent safety in children are encouraging in promoting the widespread use of contrast-enhanced US [13].

The publication regarding cardiac shunts being contraindications came to the following conclusion:

> An exhaustive review of current peer-reviewed research demonstrated no scientific basis for the ultrasound contrast agent contraindication in patients with known or suspected cardiac shunts. Initial safety concerns were based on limited rodent data and speculation related to macroaggregated albumin microspheres, a radioactive nuclear imaging agent with different physical and chemical properties and no relation to UCA. Radioactive macroaggregated albumin is not contraindicated in adult or pediatric patients with cardiac shunts and is routinely used in these populations [14].

Undoubtedly, these two publications served as important summaries for the FDA approval process of the pediatric indications.

Cost of United States Food and Drug Administration approvals

When these discussions for pediatric approval of UCAs were going on, three UCAs had already been approved for adult echocardiography in the United States (Table 1). There were no approvals for non-cardiac or pediatric indications. However, as mentioned, Bracco was undertaking a multicenter liver study in the United States for the purpose of receiving approval for its UCA for a non-cardiac indications in adults. Discussions with the three UCA manufacturers in the United States brought to light one of the stumbling blocks for submitting requests for pediatric approvals to the FDA, namely the very high application fees. In the late 1980s, individual drug reviews often took years to complete. These lengthy approval times were a significant source of frustration for patients, drug companies and the FDA itself. The FDA lacked adequate funding to review drugs in a timely manner and, as a solution, proposed collecting fees from the companies it regulates for each new product, which would provide a substantial source of funding to boost staff and reduce review times. Eventually, this led to the passage of the Prescription Drug User Fee Act (PDUFA) in 1992, which authorized the FDA to collect such fees for its review activities in return for a speedier, more predictable review process [15]. The application fee for a new drug application could be more than $2 million; a supplemental application to an already approved drug could cost $1 million. This cost is in addition to any prospective clinical trial the UCA manufacturer would need to carry out in children.

When UCA manufacturers weighed the cost involved versus the potential profit from pediatric applications, it was not

very appealing to pursue this. Only the added legal pressure from the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act would help persuade UCA manufacturers to seek pediatric approvals. Just one of the manufacturers, Bracco, was seeking additional approvals at the time. Since Bracco's initial adult-only approval of SonoVue in Europe in 2001, its off-label use in children had become widespread. SonoVue had become the most used UCA in children worldwide, described in many research publications. A PubMed search for these publications (conducted in January 2021, searching the period of 2001–2016) yielded the following number of publications per search term: (1) "contrast enhanced ultrasound" and "children" — 108, and (2) "SonoVue" and "children" — 68. A parallel search replacing "SonoVue" with "Optison" or "Definity" yielded only 10 and 13 publications, respectively, very few of which were clinical studies. Thus, it is not surprising that Bracco, with published pediatric CEUS experience and an ongoing pursuit for cardiac and non-cardiac approval in adults, was the most active in pursuing approval for pediatric indications. Certainly, the NDA solely for pediatric ceVUS was not attached to any adult application and reflects Bracco's decision to support expansion of pediatric contrast US.

Basis for United States Food and Drug Administration approval of pediatric contrast ultrasound

Understanding the underlying information and process behind the FDA approval decisions helps those actively involved in pediatric CEUS service to appropriately interpret the recommendations and perform high-quality studies. We mentioned that only the manufacturer of a UCA can request a supplemental pediatric indication for its UCA. It is also important to note that the FDA bases its decision on the submitted approval document. This means, for example, that if the approval request is for a certain route of administration or specific dose, it is this route and dose that the FDA investigates and approves or declines. Consequently, the information provided by the UCA manufacturers plays a decisive role in what ultimately appears on the package insert. The FDA documents on its website in great detail all of the information regarding not only what went into the approval process, but also post-marketing findings for each UCA.

Pediatric contrast-enhanced ultrasound of the liver

The first pediatric contrast US indication approved by the FDA came in March 2016, together with the approval for use in adults (Table 1) [16]. This was for IV administration of the UCA Lumason for liver examination to characterize focal liver lesions in adults and children. Based on FDA guidance, Bracco had conducted two identical but independent phase III clinical studies in the United States and submitted their results for the approval. Both studies in adults were titled "Characterization of focal liver lesions with SonoVue-enhanced ultrasound imaging: a phase III, intra-patient comparative study versus unenhanced ultrasound imaging using histology or combined imaging/clinical data as truth standard" [17]. A total of 499 patients with a mean age of 56 years (range 19–93 years) with at least one focal liver lesion requiring workup for characterization were included in the two studies [17]. Histology or CT/MRI served as the truth standard. Regarding the primary efficacy endpoints, Lumason-enhanced US was found to be better than non-enhanced US in the characterization of lesions as malignant or benign, corresponding to higher sensitivity and specificity. Similarly, the diagnostic performance of the Lumason-enhanced US compared to non-enhanced US demonstrated higher accuracy and positive/negative predictive values [17]. In these two studies, 2.4 mL of Lumason was administered via IV as a single bolus. Only in the case of technical failure of the first dose was a second injection of 2.4 mL of Lumason permitted [17].

Along with the submission for the approval of Lumason for liver examination in adults, Bracco included the available information about IV use of SonoVue in children, specifically referencing liver lesion characterization. The systematic literature search identified only six publications that met all the set inclusion criteria [18–23]. Only one of the six publications reported the efficacy of SonoVue-enhanced US in the characterization of focal liver lesions in the pediatric population [19]. This prospective study by Jacob et al. [19] was conducted at King's College Hospital in London, UK. Forty-four children (21 girls, 23 boys; median age 11.5 years, range 4–18 years) were included in the study. The indications were focal liver lesion in the presence of known chronic liver disease (n=30), a new focal liver lesion following treatment for a non-hepatic malignancy (n=3), and incidental finding of a focal liver lesion in children with no underlying chronic liver disease or known primary malignancy (n=11) [19]. The standards of truth were CT or MRI (n=33), histology (n=8) and 6-month or longer follow-up with non-enhanced US (n=3) [19]. SonoVue-enhanced US had a specificity of 98% (43 lesions were correctly diagnosed as benign), with a 95% confidence interval (CI) of 86–100%; the negative predictive value was 100%. One single lesion was misdiagnosed as malignant by all imaging modalities (CEUS, CT/MRI). Sensitivity could not be calculated in this study [19].

This study brought to light additional considerations. All children with an inconclusive non-enhanced US had been enrolled in this study, but it took 5 years to gather data from these 44 children at a tertiary pediatric hospital. This showed how infrequently indeterminate focal liver lesions are found on non-enhanced US in pediatric practice. Also, the study did not include any truly malignant focal liver lesions, which

again relates to the very low incidence of liver cancer in pediatric patients, and children with malignancies presented with disease that had already been characterized by CT, MRI or liver biopsy.

The IV pediatric dose from the literature was quite variable, even among the six studies that met the inclusion criteria [18–23]. The SonoVue dosage administered by Jacob et al. [19] was not weight-based but was a bolus dose ranging 1.2–2.4 mL. Thus, extrapolation from the adult dose was carried out to calculate the proposed pediatric one. It is known that blood volume is proportional to body weight at all ages. The adult dose of a single 2.4 mL dose corresponded to 0.034 mL/kg in a 70-kg person. The adult event-base dosing is 2.0 mL, i.e. 0.03 mL/kg in a 70-kg person. Consequently, Bracco proposed a dose of 0.03 mL/kg for pediatric IV liver imaging [17].

Regarding the safety of SonoVue in adults, data from 6,984 healthy volunteers and patients were provided [17]. The number of patients with at least one adverse event related to SonoVue was 369 (5.3%), mostly mild or moderate adverse events. Two (<0.1%) severe adverse events were reported and no deaths. Safety data for IV SonoVue in children were limited at the time. Bracco supported a safety pattern for children like that observed among adults by providing safety data derived from the literature from >900 pediatric patients who had been administered IV SonoVue. Seven adverse events were reported in six pediatric patients, including one serious adverse reaction of hypersensitivity. All adverse events were reported in two of the six publications, with the other four stating the absence of adverse events [18–23]. The FDA concluded that benefit/risk assessment of IV-administered Lumason demonstrated that the diagnostic benefits outweighed the potential risk. In summary, the FDA approval of Lumason for the pediatric liver indication came about by relying on a single published pediatric study for diagnostic efficacy and the safety data from the six studies described here [18–23], as well as extrapolation from the results of the U.S. multicentric study in adults [17]. The recommended dose of 0.03 mL/kg for the pediatric age group was also derived from the adult studies.

Pediatric contrast-enhanced ultrasound of the urinary tract

Nine months after the pediatric approval of IV Lumason for hepatic indications, the FDA went on to approve the same UCA for intravesical administration for evaluation of suspected or known vesicoureteric reflux (VUR) in children (Table 1). This was a major milestone. Since the mid-'90s, ceVUS had been the most widespread contrast US examination in children worldwide, and particularly in Europe. Following the FDA's suggestion, Bracco submitted a compilation of existing scientific data for the approval of this indication [24]. A literature search identified four prospective pediatric ceVUS studies that used the same dose of SonoVue, i.e. a flat dose of 1 mL [25–28]. The identical dosing in these studies was the baseline for compiling the data in a meta-analysis. The 1-mL single-bolus dose translates to 1.3% to 0.4% of the bladder capacity in pediatric patients ages 6 months to 6 years, respectively, an age group in which ceVUS is frequently performed. It is important to note that the four studies included for analysis were conducted before 2014. Since then, US scanners have significantly improved contrast-specific imaging modality, with increased capability to conspicuously depict the microbubbles. With this current technology, a 1-mL intravesical bolus might turn out to be too high a dose for ceVUS. Another important fact to note is that the alternative use of a normal saline-UCA suspension infusion, which is potentially a more optimal way of filling the bladder, was not at all considered in this approval because the selected four studies did not incorporate this method [29].

A meta-analysis of these four comparative studies [25–28] with voiding cystourethrography (VCUG) examined the diagnostic performance of SonoVue-enhanced VUS [24]. A total of 508 pediatric patients (275 boys, 233 girls; age range 2 days–13 years) with 1,023 pelvi-ureter units were included in the meta-analysis. The pooled results and 95% CI for sensitivity and specificity were 89% (80–97%) and 81% (76–86%), respectively, for ceVUS compared to VCUG. Safety data from 13 publications on SonoVue-enhanced VUS, which encompassed more than 6,000 children (age range 2 days to 18 years), were submitted for the approval; a detailed report regarding the safety analysis can be found at [24]. Transient non-serious adverse events were reported within 2–24 h after the ceVUS, such as dysuria, crying, anxiety, abdominal pain, frequency, hematuria and urinary tract infection, but these were all likely more related to the bladder catheterization than the UCA. The FDA granted the approval after evaluating the diagnostic efficacy and safety of SonoVue-enhanced VUS based on published data, recommending the dose of a 1-mL bolus as used in the evaluated four ceVUS studies [25–28].

Pediatric contrast echocardiography

The third and most recent approval for a new pediatric indication came in November 2019 for Lumason's use in echocardiography, as mentioned (Table 1). This was supported by the Pediatric Research Equity Act post-marketing requirement study in the United States. The initial plan for the study was to enroll 92 patients, but this proved difficult, and the study was conducted with only 12 subjects (5 boys, 7 girls; mean age 13.8 years, range 9–17 years) evaluated at two sites in the United States [30]. The same dose as for the liver examination, 0.03 mL/kg body weight, was used for the echocardiography. The indication was suboptimal non-enhanced echocardiogram for better left ventricular opacification and endocardial borders delineation. The contrast echocardiogram converted a

significant number of suboptimal non-enhanced echocardiograms to optimal diagnostic studies regarding endocardial borders delineation ($P<0.0001$) [30]. Safety data from this study in addition to published data from pediatric liver CEUS studies and other adult reports served as the basis for the FDA's decision to approve UCA as safe for pediatric echocardiography. As expected, contrast echocardiography used the same route and dose of administration as the pediatric liver examination, the adverse events encountered with contrast echocardiography were similar. At the time of submission for the pediatric contrast echocardiography approval, there was no experience in children younger than 9 years. Based on a survey of pediatric cardiologists and a literature search, the FDA extended approval for the UCA to include all pediatric age groups. The conclusion in the clinical review of NDA 203684 s005 by the FDA [30] reads as follows:

> This efficacy supplement to extend the echocardiography indication from adults to pediatrics is approvable based on extrapolation from adult data as supported by new pediatric evidence provided by study BR1-140. While we do not directly have use data from the 0 to 9-year age group…, there are no specific safety concerns for the use of Lumason in children under 9 years of age for echocardiography. Given the published literature of the safety of intravenous use of Lumason in pediatric patients, including those under 9 years of age, and the fact that the drug is already approved for all pediatric age groups for the liver lesion indication, the pediatric echocardiography indication should be extended to pediatric patients of all ages.

Activities post-pediatric Food and Drug Administration approvals

Along with the approval for intravesical use of Lumason for vesicoureteric reflux evaluation, the FDA decided to remove the cardiac shunt contraindication, i.e. known or suspected right-to-left, bi-directional or transient right-to-left cardiac shunts, from the label packaging insert [31]. The ICUS's publication on this topic appears to have been instrumental in this change [14].

In Europe, since 2001 SonoVue had been approved for adult IV indications. At the same time there was widespread use of SonoVue for off-label ceVUS examinations in children. Despite its pediatric application for more than two decades in Europe, it was only after the approval in the United States that the European Medicines Agency gave in June 2017 the pediatric approval for SonoVue use for ceVUS in children [32]. Interestingly, the European approval for ceVUS stipulated that Bracco conduct a post-authorization efficacy study [33]. In fact, to date the IV use of the UCAs in children is not approved in Europe.

Shortly after the FDA approvals for the liver and urinary tract pediatric indications, on May 2, 2017, the second joint SPR–ICUS professional society briefing of the FDA regarding pediatric contrast US took place, where Kassa Darge, MD, PhD, presented an update on pediatric CEUS. The following three issues were emphasized: (1) FDA approval of pediatric indications had made a tremendous positive impact in advancing CEUS in the United States, (2) CEUS in children was expanding beyond liver and reflux and (3) an important newly increasing application of CEUS was in pediatric interventional US. The joint briefing included discussion of two additional major issues. One was the potential need for a whole-body indication approval in light of expanding off-label applications to different organs. The practical difficulty of putting together an application for such an approval was pointed out (FDA, May 2017, personal communication). Nevertheless, it was understood that this would be a recurring theme considering the expansion of off-label use. The other point discussed was the removal of the black box warning from all UCAs. A black box warning is the FDA's strictest warning for drugs and medical devices on the market. These warnings alert consumers and health care providers to potential serious side effects [34]. The FDA had announced the addition of the black box warning for all UCAs on Oct. 10, 2007 [35]. Seven years later, when Lumason was approved for the first time by the FDA, the black box warning was also added to it. Thus, all three UCAs approved in the United States (Optison, Definity, Lumason) had the black box warning in their package insert contraindicating their administration in people with worsening or clinically unstable heart failure, coronary syndromes or acute myocardial infarction.

This discussion was the impetus for the ICUS submitting a citizen petition in September 2018, updated in August 2020, for the removal of the boxed warnings from the UCA product labels [36]. The ICUS argued:

> The UCA boxed warnings followed spontaneous reports of a small number of serious adverse events that occurred after UCA administration. However, the reported serious adverse events 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 UCA are exceedingly safe, efficacious and save lives.

The citizen petition has garnered support of numerous professional ultrasound societies and CEUS experts. For example, a statement submitted to the FDA by the American Institute of

Ultrasound in Medicine (AIUM) stated, in part: "FDA's prolonged 'black box' warning hinders the delivery of optimal diagnostic imaging services to our patients." At the time of this writing, the ICUS citizen petition remained under review.

Ongoing activities of the Contrast-Enhanced Ultrasound Task Force

Since its establishment almost a decade ago, the CEUS Task Force has made significant impact in advancing pediatric CEUS through its advocacy, extensive educational undertakings and support of pediatric contrast US research as laid out in its objectives (Table 2). The task force's collaboration with the ICUS to advocate for pediatric approvals by the FDA resulted in approvals for three pediatric indications. The great impact of these approvals for widespread contrast US use in the United States cannot be sufficiently stressed. But long before these approvals, the CEUS Task Force had begun education programs, using primarily the educational platforms of the ICUS, SPR and AIUM. The educational activities were expanded post-approval through hands-on courses offered by the ICUS and pediatric-focused ones by the Center for Pediatric Contrast Ultrasound (CPCU) at Children's Hospital of Philadelphia [37]. The CEUS Task Force conducted a national survey, the results of which revealed the need for education on pediatric CEUS [38]. Furthermore, the webpages of the CEUS Task Force on the SPR website continue to develop, incorporating useful and practical information on pediatric CEUS [39].

Five years elapsed between the constitution of the CEUS Task Force and the first pediatric approval of a UCA. During that time, because the task force members did not know whether or when a pediatric approval would take place, they decided to support off-label use and FDA-approved investigational new drug studies. At that early stage, only Optison and Definity were available, and Lumason had not been approved. The task force evaluated pediatric studies published using Optison and Definity in the United States and found that the few CEUS studies that included pediatric safety evaluations were conducted using Optison at St. Jude Children's Research Hospital, Memphis, TN, by M. Beth McCarville, MD, and collaborators [40]. Consequently, prior to the FDA pediatric approval, the CEUS Task Force advocated for the use of just one UCA, Optison, because the limited available pediatric data were more readily available for this UCA than for Definity. It was believed that the focus on one UCA would eventually support the execution of multi-center pediatric CEUS studies and the gathering of more diagnostic efficacy and safety experience. Thus, one of the first investigational new drugs approved by the FDA for a prospective pediatric CEUS study was for ceVUS with intravesical administration of Optison in children [41].

Conclusion

Since 2016, the FDA has approved the UCA Lumason for three pediatric indications. These approvals, granted almost 20 years after the FDA first approved a UCA for adult imaging, grew out of the dedicated advocacy efforts of the ICUS and the SPR CEUS Task Force, the FDA's strong commitment to the welfare of pediatric patients, and the compelling research and clinical experiences of pediatric CEUS thought leaders and practitioners. To an extent, the approvals also might have been occasioned by fortuitous timing because regulators and policymakers were increasingly concerned about radiation-based imaging of children. The result has profoundly impacted pediatric UCA utilization, not just in the United States but worldwide. Indeed, pediatric CEUS is now included in imaging guidelines and recommendations promulgated by several independent professional societies [42–44]. These documents reflect the growing awareness of the clinical settings in which UCAs can help improve diagnostic imaging of children. Further, pediatric CEUS education is growing, as are peer-reviewed reports of the safety and clinical benefits of this important imaging modality for children. A PubMed search using the phrases "contrast enhanced" and "ultrasound" with the filter "child: birth-18 years" from 1995 to 2015, i.e. over a period of 20 years, yielded 1,706 citations (conducted February 2021). Using the same phrases, a search of publications from 2016 to 2021, a mere 5 years post-pediatric indication approval, yielded 903 citations. In other words, post-approval, the number of publications is 50% of what was produced in the preceding two decades. Pediatric CEUS has indeed come a long way in a short span of time in the United States!

Declarations

Conflicts of interest Drs. Darge and Back have received education grants from Bracco Diagnostics Inc., participate in educational activities and are part of the CEUS course faculty at the Children's Hospital of Philadelphia. Dr. Feinstein is a speaker for GE Healthcare (ultrasound) and Bracco. Dr. McCarville receives product support from GE Healthcare, Bracco and Philips.

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