Clinical Pharmacology Review	
NDA	203-684; SE-1
Submission Date	June 4, 2015 (SDN 40) November 6, 2015 (SDN 58) November 18, 2015 (SDN 59)
Brand Name	Lumason (sulfur hexafluoride lipid type A microbubbles injection; SF6)
Formulation	Suspension for Injection
OCP Reviewer	Christy S John, Ph.D.
OCP Team Leader	Gene M. Williams, Ph.D.
OCP Division	Division of Clinical Pharmacology V
OND Division	Division of Medical Imaging Products
Applicant	Bracco Diagnostics, Inc.
Submission Type; Code	Supplement-1 (Efficacy)
Dosing regimen	Ultrasonography of the Liver: Recommended dose after reconstitution is 2.4 mL in adults (b) (4) patients, administered as an intravenous bolus injection. During a single examination, a second injection of 2.4 mL in adults (b) (4), may be administered if necessary.
Indication	Lumason is an ultrasound contrast agent indicated for use: in adult patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border; **and in adult and pediatric patients,** (b) (4) **characterization of focal liver lesions. (**The indication in **red** is the new indication proposed by the sponsor.)

Table of Contents

1 EXECUTIVE SUMMARY

The indication in bold is the new proposed indication for this efficacy supplement.
"Lumason is an approved ultrasound contrast agent indicated for use: in adult patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border; **and in adult and pediatric patients** (b) (4) **characterization of focal liver lesions.**"

The package insert dose for the approved endocardial border delineation indication is 2.0 mL. The applicant performed two dose findings studies in patients with focal liver lesions (FLL) to determine the dose to be carried forward in studies for the current indication ((b) (4) characterization of FLL). Three doses were investigated: 0.6 ml, 1.2 mL and 2.4 mL. Although the differences in imaging between the dose groups were limited, it appeared that the 2.4 mL dose may perform better than the two lower doses. Safety issues across the dose range were insignificant – there was no dose-response relationship for adverse events. The 2.4 mL dose was selected for use in the focal liver lesion studies.

The applicant conducted two multicenter, Phase III studies in adult patients. For both studies, the sensitivity and specificity of Lumason for FLL was superior to unenhanced ultrasound, using final diagnosis based on histology or combined imaging (contrast enhanced computed tomography (CE-CT) and/or contrast-enhanced magnetic resonance imaging (CE-MRI)) as the truth standard. The applicant's proposed focal liver lesion indication includes pediatric patients, with no lower age restriction, but the applicant did not conduct an efficacy study in the pediatric population. Efficacy and safety in pediatric patients is based upon literature data.

The proposed package insert recommended that children be dosed (b) (4) In response to an information request, the applicant proposed two alternative dosing regimens for FDA's consideration, a) (b) (4) b) a dose of 0.03 mL/kg, (b) (4) pediatric patients. The reviewer recommends that the single weight based dose (0.03 mL/kg = 2mL/70 kg = 0.034 mL/kg ≈ 0.03 mL/kg) be used for pediatric patients if the indication is granted. This recommendation is based on the apparent restriction of sulfur hexafluoride microbubbles (SF6) to the blood compartment, and the established allometric relationship that the volume of the blood compartment scales to body size across pediatric ages. (b) (4)

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed Efficacy Supplement 1 for NDA 203-684 (SE-1) and recommends approval of the application, provided an agreement can be reached on pediatric dosing and labeling.

Drug Development Decision	**Sufficiently Supported?**	**Recommendations and Comments**
Overall	☑Yes ☐No	
Evidence of effectiveness	☑Yes ☐No Refer to Section 2.2.2	Based on two clinical safety and efficacy trials.
Proposed dose for general population	☑Yes ☐No Refer to Section 2.2.7	Empirically based: efficacy demonstrated, adverse events minimal.
Proposed dose selection for others	☑Yes ☐No Refer to Section 2.3.2	A dose of 0.03 mL/kg for (b) (4) pediatric patients. Negotiated with applicant during review cycle.
Labeling	☑Yes ☐No Refer to Section 3.0	Minor edits to **2.1 Recommended Dose** / 2.1.2 Ultrasonography of the Liver and **12.2 Pharmacodynamics**

Labeling Recommendations

Refer to Section **3 DETAILED LABELING RECOMMENDATIONS**.

1.2 Post-Marketing Requirements and Commitments

No post-marketing requirements or commitments are recommended.

1.3 Summary of Clinical Pharmacology Findings

The currently approved indication for Lumason is for adults only, "Lumason is an ultrasound contrast agent indicated for use in adult patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border." The proposed new indication is, "in adult and pediatric patients, (b) (4) characterization of focal liver lesions."

The package insert dose for the approved endocardial border delineation indication is 2.0 mL. The applicant performed two dose findings studies to determine the dose to be carried forward in studies for the current indication ((b) (4) characterization of focal liver lesions or FLL). Three doses were investigated: 0.6 ml, 1.2 mL and 2.4 mL. Although the differences in imaging between the dose groups were limited, it appeared that the 2.4 mL dose may perform better than the two lower doses. Safety issues across the dose range were insignificant – there was no dose-response relationship for adverse events. The 2.4 mL dose was selected for use in the focal liver lesion studies.

The applicant conducted two multicenter, Phase III studies. For both studies, the sensitivity and specificity of Lumason for FLL was superior to unenhanced ultrasound, using final diagnosis based on histology or combined imaging (contrast enhanced computed tomography (CE-CT) and/or contrast-enhanced magnetic resonance imaging (CE-MRI)) as the truth standard.

The applicant's proposed focal liver lesion indication includes pediatric patients, with no lower age restriction, but the applicant did not conduct an efficacy study in the pediatric population. Six literature articles were submitted to justify the efficacy and safety of Lumason in the pediatric population. There are no PK data in the literature cited, nor did the reviewer's literature search reveal pediatric PK data. Therefore, pediatric dosing decisions must be based on the mechanism of action of the drug, physiological considerations, and the doses used in the literature cited.

An article by Jacob J, et al. was the primary basis for assessment of pediatric efficacy. Jacob et al. found that specificity was 98% (43 lesions were correctly diagnosed as benign), with a 95% CI of 86-100%; the negative predictive value was 100%. One single lesion was misdiagnosed as malignant by all imaging modalities (CE-US, CT/MRI). The low true positive rate does not allow sensitivity to be calculated in this study.

The proposed package insert recommended that children be dosed (b) (4) . In an information request (IR) for the raw data in the Jacob et al. and Piskunowicz et al. publications, FDA suggested that lower doses may be appropriate for pediatric patients. The applicant proposed two alternatives for FDA's consideration, a) (b) (4) b) a dose of

0.03 mL/kg, [redacted] pediatric patients. The reviewer recommends that the single weight based dose (0.03 mL/kg = 2mL/70 kg = 0.034 mL/kg ≈ 0.03 mL/kg) be used for pediatric patients. Following intravenous injection, distribution of SF6 appears to be restricted to blood. As blood volume is proportional to body weight in both adults and pediatric patients, weight based dosing should be bette [redacted]

Because efficacy data in children under 4 years of age are not available, the reviewer considered whether they should receive an alternative dose. Based on the apparent restriction of SF6 to the blood compartment, and the established allometric relationship that the volume of the blood compartment scales to body size across pediatric ages, one would predict that children under 4 will not need an alternative dose.

SIGNATURES

Reviewer: Christy S John, Ph.D.
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2 QUESTION BASED REVIEW

2.1 GENERAL ATTRIBUTES

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

2.1.2 What are the proposed mechanisms of action and therapeutic indications?

Lumason is an ultrasound contrast agent indicated for use in adult patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border. The new indication for this efficacy supplement is for use "in adult and pediatric patients (b) (4) characterization of focal liver lesions."

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The applicant conducted two multicenter, Phase III studies. The primary objective of both studies (BR1-128 (N=240) and BR1-130 (N=259)) was to demonstrate that the sensitivity and specificity of Lumason-enhanced ultrasound for the characterization of benign versus malignant focal liver lesions (FLLs) were superior to unenhanced ultrasound, using final diagnosis based on histology or combined imaging (contrast enhanced computed tomography (CE-CT) and/or contrast-enhanced magnetic resonance imaging (CE-MRI)) as the truth standard. The mean volume of Lumason administered in both studies was 2.6 mL. Of the subjects who received Lumason, 7.6% received Lumason bolus injection a second time due to failure of ultrasound machine, extravasation etc. The diagnostic performance of Lumason in Study BR-128 is shown in **Table 1.** With the exception of one reader (one reader has higher sensitivity for unenhanced), sensitivity, specificity and accuracy were higher for contrast enhanced ultrasound (CE-US) than for unenhanced ultrasound (UE-US). The diagnostic performance of Lumason in Study BR-130 is shown in **Table 2.** For each reader, sensitivity, specificity and accuracy were higher for contrast enhanced ultrasound (CE-US) than for unenhanced ultrasound (UE-US).

Table 1. Study BR1-128, Diagnostic performance of Lumason enhanced ultrasound (CE-US) vs unenhanced ultrasound (UE-US).

	Off-site Reader 1 (N=240)		Off-site Reader 2 (N=240)		Off-site Reader 3 (N=240)		On-site (N=240	
Parameter	UE-US	CE-US	UE-US	CE-US	UE-US	CE-US	UE-US	CE-US
Sensitivity (%)	53.2	64.5	41.1	60.5	66.1	46.8	33.9	87.9
Specificity (%)	24.1	71.6	6.9	67.2	58.6	87.9	24.1	90.5
Accuracy (%)	39.2	67.9	24.6	63.8	62.5	66.7	29.2	89.2

Table 2. Study BR1-130, Diagnostic performance of Lumason enhanced ultrasound (CE-US) vs unenhanced ultrasound (UE-US).

	Off-site Reader 1 (N=259)		Off-site Reader 2 (N=259)		Off-site Reader 3 (N=259)		On-site (N=259	
Parameter	UE-US	CE-US	UE-US	CE-US	UE-US	CE-US	UE-US	CE-US
Sensitivity (%)	48.7	86.6	35.3	75.6	16.0	91.6	40.3	90.8
Specificity (%)	62.9	70.7	54.3	82.9	22.1	72.9	19.3	78.6
Accuracy (%)	56.4	78.0	45.6	79.5	19.3	81.5	29.0	84.2

Of the 2939 patients who received Lumason in the completed liver studies, 180 patients

(6.1%) experienced 282 adverse events; the events were reported as study agent-related for 74 patients (2.5%). All but 3 adverse events were mild or moderate in intensity, 3 events were of severe intensity. The adverse events were not related to drug dose administered.

2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD) and how are they measured in clinical pharmacology and clinical studies?

No clinical studies with pharmacokinetics were submitted with this efficacy supplement.

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Not applicable – the current sNDA has no pharmacokinetics or other data where concentrations in human biomatrices were measured.

2.2.4 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?
2.2.5 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

See section **2.2.7.**

2.2.6 Does this drug prolong the QT or QTc interval?

There was no signal for QT prolongation in the original NDA (see review of Original NDA203-684, DARRTS date August 24, 2012).

There are no significant changes in QT or QTc after the administration of Lumason. QTc interval increased ≤30 msec for 47.1% of patients and increased ≥60 msec from baseline for 0.6% patients. Similarly, QTc interval decreased ≤30 msec for 40.7% of patients and decreased ≥60 msec from baseline for 0.8% of patients.

2.2.7 Is the dose and dosing regimen selected by the applicant consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The applicant's proposed package insert adult dose for the new indication is 2.4 ml. The recommended dose for the approved indication of endocardial border delineation is 2.0 mL.

As part of the development program for focal liver lesion characterization, two trials examining effectiveness across doses were performed. Results are shown in **Table 3**.

Table 3. Results from studies evaluating alternative doses

Protocol No	No of Patients	Study Design	SonoVue Dose (Efficacy Population; N malignant/N benign)	Gold Standard	Sensitivity		Specificity		Accuracy	
					UE-US	CE-US	UE-US	CE-US	UE-US	CE-US
BR1-071	185 for efficacy	USA dose-finding, parallel groups, FLL characterization of indeterminate target lesion (onsite assessment)	0.6 mL (63 eff ; 25M/38B) 1.2 mL (63 eff; 26M/37B) 2.4 mL (59 eff; 21M/38B)	Final diagnosis Histology/ CT/MRI	48% 46% 43%	84% 85% 90%	32% 16% 24%	63% 76% 82%	38% 29% 31%	71% 79% 85%
BR1-072	207 for efficacy	USA dose-finding, parallel groups, FLL characterization of indeterminate target lesion (onsite assessment)	0.6 mL (63 eff; 29M/34B) 1.2 mL (73 eff; 30M/43B) 2.4 mL (71 eff; 35M/36B)	Final diagnosis Histology/ CT/MRI	41% 27% 43%	66% 83% 83%	21% 23% 25%	88% 91% 81%	30% 25% 34%	78% 88% 82%

FLL, focal liver lesion; UE-US, unenhanced ultrasound; CE-US, contrast-enhanced ultrasound; eff, efficacy; M, malignant; B, benign; CT, computed tomography; MRI, magnetic resonance imaging

On the basis of these data, the applicant performed the efficacy and safety studies that are the basis of approval (see **2.2.1**) using the 2.4 mL dose. Although the differences between dose groups are limited, it does appear that the 2.4 mL dose may perform better than the two lower doses. Safety issues across the dose range were insignificant – there was no dose-response relationship for adverse events.

2.2.8 What are the single dose PK parameters?
2.2.9 What are the characteristics of drug distribution?
2.2.10 Does the mass balance study suggest renal or hepatic as the major route of elimination?
2.2.11 What are the characteristics of drug metabolism?
2.2.12 What are the characteristics of drug excretion?
2.2.13 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?
2.2.14 Based on PK parameters, what is the degree of linearity or non-linearity based in the dose-concentration relationship?
2.2.15 How do the PK parameters change with time following chronic dosing?
2.2.16 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

See review of Original NDA203-684 (DARRTS date August 24, 2012). No clinical studies with pharmacokinetics were submitted with this efficacy supplement.

2.3 INTRINSIC FACTORS

2.3.1 Do intrinsic factors (race, gender, age, body weight, tumor type, genetic polymorphisms, renal function, and hepatic function) influence the PK and are dose adjustments needed based on these intrinsic factors?

See review of Original NDA203-684 (DARRTS date August 24, 2012).
Six literature articles were submitted to justify the efficacy and safety of Lumason for FLL in the pediatric population. There are no PK data in the literature cited, nor did the reviewer's literature search reveal pediatric PK data.

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dose adjustments, if any, are recommended for each of these groups? If dose adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

The proposed indication includes pediatric patients, with no lower age restriction, but the applicant did not conduct an efficacy study in the pediatric population. There are no PK data in the literature cited, nor did the reviewer's literature search reveal pediatric PK data. Therefore, pediatric dosing decisions must be based on the mechanism of action of the drug, physiological considerations, and the doses used in the literature cited.

Six literature articles were submitted to justify the efficacy and safety of Lumason in the pediatric population. Two of the articles (Jacob J, et al. and Piskunowicz M, et al.) form the primary basis for assessment. Data from the two studies were combined to construct **Figure 1**. and **Figure 2**.

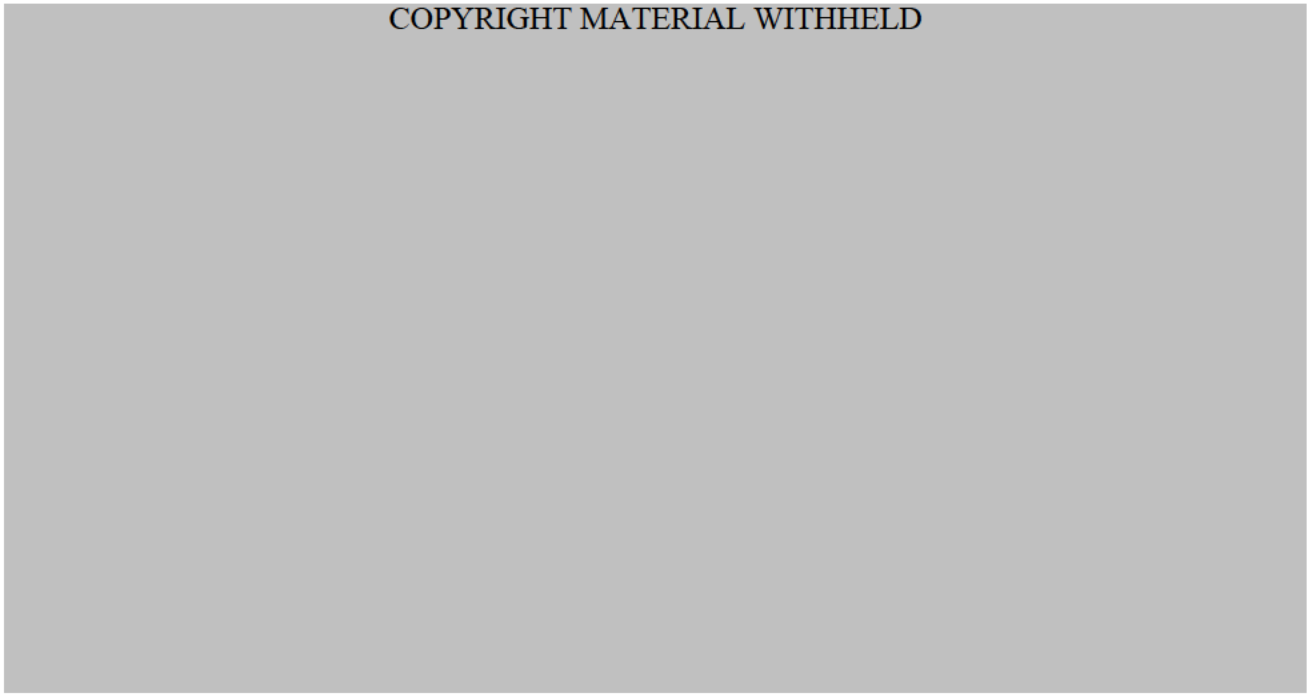
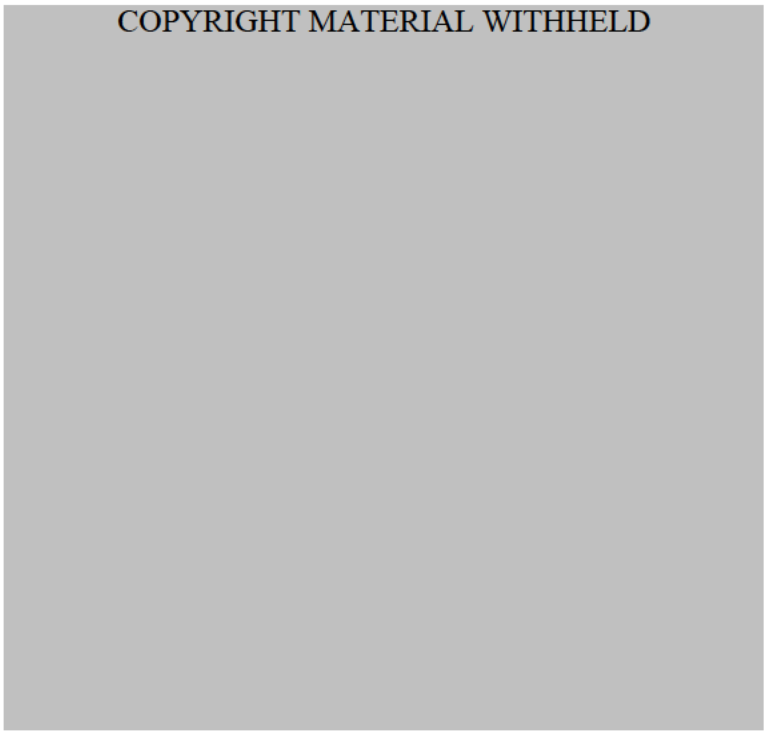


Figure 3. shows dose as function of age for each of the studies.. This breakdown by study is included because only Jacob et al. (left panel) is relevant for efficacy.

Figure 3. Dose (ml/kg) vs weight in pediatric studies



Jacob et al. and Piskunowiz et al. are reviewed independently, below.

Jacob et al. (Jacob J, et al. Contrast enhanced ultrasound (CEUS) characterization of grey-scale sonographic indeterminate focal liver lesions in pediatric practice. Ultraschall Med. 2013;34:529-40).

SonoVue (Lumason) was injected as a bolus at the dose of 1.2 or 2.4 mL followed by 10 mL of normal saline flush via an arm vein cannula previously sited by an experienced pediatrician.

44 children (21 female, 23 male; median age 11.5yrs; range 4 – 18yrs) were included in the study. The predominant reason for referral was the presence of a FLL in a child with known chronic liver disease (n = 30) followed up with ultrasonography, a new FLL (n = 3) following treatment for a non-hepatic malignancy, and incidental finding of a FLL in children with no underlying chronic liver disorder or known primary malignancy (n = 11). The article reports that no adverse events occurred. Standard of truth for FLL characterization in the 44 patient studies was:

- CT and/or MR imaging (n = 33 patient studies);
- Histology following lesional/excisional biopsy or liver transplantation (n = 8);
- Follow-up (6-month or longer) with plain ultrasonography (n = 3).
- The background liver was subject to biopsy in 14 patients showing liver steatosis (n = 9) or cirrhosis (n = 5).

Based on the final diagnosis, specificity was 98% (43 lesions were correctly diagnosed as benign), with a 95% CI of 86-100%; the negative predictive value was 100%. One single lesion was misdiagnosed as malignant by all imaging modalities (CE-US, CT/MRI). The low true positive rate does not allow sensitivity to be calculated in this study.

No child under 4 years of age was studied by Jacobs et al. Selection of a dose for children will be discussed at the conclusion of this section, under the sub-heading Pediatric Dosing.

Piskunowicz M, et al. Safety of intravenous application of second-generation ultrasound contrast agent in children: prospective analysis. Ultrasound Med Biol. 2015; 41:1095-9

This publication regarded safety (not efficacy) and dosing of ultrasound imaging contrast agents. The dose of Lumason used in this study ranged from (0.1 – 1.8 mL). 137 children (83 female, 54 male; median age 11.1 yrs; range 31 days to 17.9 years) were included in the study. The article reported only one adverse event: a hypersensitivity reaction occurred following 0.6 mL of Lumason in an 11-year-old girl (weight: 28.5 kg, height: 138 cm). Forty-three seconds after intravenous administration of 0.6 mL Lumason, the patient developed symptoms of anaphylactic shock. The reviewer notes that hypersensitivity reactions are generally not dose-dependent.

Pediatric Dosing

There are no pharmacokinetic data in children to bridge children to adults or children under 4 to older children or adults.

The proposed package insert recommended that children be dosed [redacted] (b) (4) . In an information request (IR) for the raw data in the Jacob et al. and Piskunowicz et al. publications, FDA suggested that lower doses may be appropriate for pediatric patients. The applicant proposed two alternatives for FDA's consideration, a) [redacted] (b) (4) b) a dose of 0.03 mL/kg, [redacted] (b) (4) pediatric patients. The reviewer recommends that the single weight based dose (0.03 mL/kg = 2mL/70 kg = 0.034 mL/kg ≈ 0.03 mL/kg) be used for pediatric patients. Following intravenous injection, distribution of SF6 appears to be restricted to blood. As blood volume is proportional to body weight in both adults and pediatric patients, weight based dosing should be better [redacted] (b) (4)

Because efficacy data in children under 4 years of age are not available, the reviewer considered whether they should receive an alternative dose. Based on the apparent restriction of SF6 to the blood compartment, and the established allometric relationship that the volume of the blood compartment scales to body size, one would predict that children under 4 will not need an alternative dose. If the Medical Officer concludes that the efficacy data in children 4 and older and adults supports an indication for children under 4, the 0.03 mL/kg dose is recommended for younger (as well as older) children.

2.4 EXTRINSIC FACTORS

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

2.4.2 Is there an *in vitro* basis to suspect *in vivo* drug-drug interactions?

2.4.3 Is the drug a substrate of CYP enzymes?

2.4.4 Is the drug an inhibitor and/or an inducer of CYP enzymes?

2.4.5 Is the drug a substrate of P-glycoprotein (P-gp) transport processes?

2.4.6 Are other metabolic/transporter pathways important?

2.4.7 Does the label specify co-administration of another drug and, if so, has the interaction potential between these drugs been evaluated?

2.4.8 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

See review of Original NDA203-684 (DARRTS date August 24, 2012). No clinical studies with pharmacokinetics were submitted with this efficacy supplement.

2.5 GENERAL BIOPHARMACEUTICS

2.5.1 Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?
2.5.2 What is the composition of the to-be-marketed formulation?
2.5.3 What moieties should be assessed in bioequivalence studies?
2.5.4 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?
2.5.5 Has the applicant developed an appropriate dissolution method and specification that will assure *in vivo* performance and quality of the product?

See review of Original NDA203-684 (DARRTS date August 24, 2012. The current sNDA has no issues related to biopharmaceutics.

2.6 ANALYTICAL SECTION

2.6.1 Were relevant metabolite concentrations measured in the clinical pharmacology and biopharmaceutics studies?
2.6.2 Which metabolites have been selected for analysis and why?
2.6.3 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?
2.6.4 What bioanalytical methods are used to assess concentrations? (Refer to the guidance for industry on Bioanalytical Method Validation, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070107.pdf)
2.6.5 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

Not applicable – the current sNDA has no pharmacokinetics or other data where concentrations in human biomatrices were measured.

3 DETAILED LABELING RECOMMENDATIONS

Clinical pharmacology related sections of the applicant's proposed package insert, together with FDA's most current revisions, begin on the following page of this review. FDA's edits may undergo further revision, as they have not been conveyed to and negotiated with the applicant.

APPLICANT'S PROPOSED VERSION Changes from prior approved version shown as tracked changes	REVIEWER'S RECOMMENDATIONS Changes from **APPLICANT'S PROPOSED VERSION** shown as tracked changes
2 DOSAGE AND ADMINISTRATION **2.1 Recommended Dose** 2.1.2 Ultrasonography of the Liver Adults: The recommended dose of Lumason after reconstitution is 2.4 mL administered as an intravenous bolus injection during ultrasonography of the liver. During a single examination, a second injection of 2.4 mL may be administered if (b) (4) . Follow (b) (4) Lumason injection with an intravenous flush using 5 mL of 0.9% Sodium Chloride Injection. Pediatric patients: The recommended dose of Lumason after reconstitution (b) (4) administered as an intravenous (b) (4) injection during ultrasonography of the liver. During a single examination, a second injection of (b) (4) may be administered if (b) (4) Follow (b) (4) Lumason injection with an intravenous flush (b) (4) of 0.9% Sodium Chloride Injection. **12 CLINICAL PHARMACOLOGY** **12.1 Mechanism of Action** Within the blood, the acoustic impedance of Lumason microspheres is lower than that of the surrounding non-aqueous tissue. Therefore, an ultrasound beam is reflected from the interface between the microspheres and the surrounding tissue. The reflected ultrasound signal provides a visual image that shows a contrast between the blood and the surrounding tissues.	**2 DOSAGE AND ADMINISTRATION** **2.1 Recommended Dose** 2.1.2 Ultrasonography of the Liver Adults: The recommended dose of Lumason after reconstitution is 2.4 mL administered as an intravenous bolus injection during ultrasonography of the liver. During a single examination, a second injection of 2.4 mL may be administered (b) (4) . Follow (b) (4) Lumason injection with an intravenous flush using 5 mL of 0.9% Sodium Chloride Injection. Pediatric patients: The recommended dose of Lumason after reconstitution is 0.03 mL/kg administered as an intravenous (b) (4) injection during ultrasonography of the liver. During a single examination, a second injection of 0.03 mL/kg may be administered if (b) (4) . Follow each Lumason injection with an intravenous flush (b) (4) of 0.9% Sodium Chloride Injection **12 CLINICAL PHARMACOLOGY** **12.1 Mechanism of Action** Within the blood, the acoustic impedance of Lumason microspheres is lower than that of the surrounding non-aqueous tissue. Therefore, an ultrasound beam is reflected from the interface between the microspheres and the surrounding tissue. The reflected ultrasound signal provides a visual image that shows a contrast between the blood and the surrounding tissues.

12.2 Pharmacodynamics (b) (4) Lumason provides useful echocardiographic signal intensity for two minutes after the injection. (b) (4) Lumason microspheres are destroyed and contrast enhancement decreases as the MI increases. For ultrasonography of the liver, (b) (4) Lumason provides dynamic (b) (4) patterns of differential signal intensity enhancement between focal liver lesions and liver parenchyma during the arterial, portal venous, and late phase of signal intensity enhancement of the microvasculature. **Pharmacokinetics** The pharmacokinetic of the SF6 gas component of Lumason was evaluated in 12 healthy adult subjects (7 men and 5 women). After intravenous bolus injections of 0.03 mL/kg and 0.3 mL/kg of Lumason, corresponding to approximately 1 and 10 times the recommended doses, concentrations of SF6 in blood peaked within 1 to 2 minutes for both doses. The terminal half-life of SF6 in blood was approximately 10 minutes for the 0.3 mL/kg dose. (At the 0.03 mL/kg dose, terminal half-life could not be estimated.) The area-under-the-curve of SF6 was dose-proportional over the dose range studied.	**12.2 Pharmacodynamics** (b) (4) Lumason provides useful echocardiographic signal intensity for two minutes after the injection. (b) (4) umason microspheres are destroyed and contrast enhancement decreases as the MI increases (values of 0.8 or less are recommended). For ultrasonography of the liver, (b) (4) of Lumason provides dynamic (b) (4) ~~patterns of differential signal intensity enhancement between focal liver lesions and liver parenchyma during the arterial, portal venous, and late phase of signal intensity enhancement of the microvasculature~~. **Pharmacokinetics** The pharmacokinetic of the SF6 gas component of Lumason was evaluated in 12 healthy adult subjects (7 men and 5 women). After intravenous bolus injections of 0.03 mL/kg and 0.3 mL/kg of Lumason, corresponding to approximately 1 and 10 times the recommended doses, concentrations of SF6 in blood peaked within 1 to 2 minutes for both doses. The terminal half-life of SF6 in blood was approximately 10 minutes for the 0.3 mL/kg dose. (At the 0.03 mL/kg dose, terminal half-life could not be estimated.) The area-under-the-curve of SF6 was dose-proportional over the dose range studied.

Distribution In a study of healthy subjects, the mean values for the apparent steady-state volume of distribution of SF6 were 341 L and 710 L for Lumason doses of 0.03 mL/kg and 0.3 mL/kg, respectively. Preferential distribution to the lung is likely responsible for these values. **Elimination** The SF6 component of Lumason is eliminated via the lungs. In a clinical study that examined SF6 elimination twenty minutes following Lumason injection, the mean cumulative recovery of SF6 in expired air was 82 ± 20% (SD) at the 0.03 mL/kg dose and 88 ± 26% (SD) at the 0.3 mL/kg dose.	**Distribution** In a study of healthy subjects, the mean values for the apparent steady-state volume of distribution of SF6 were 341 L and 710 L for Lumason doses of 0.03 mL/kg and 0.3 mL/kg, respectively. Preferential distribution to the lung is likely responsible for these values. **Elimination** The SF6 component of Lumason is eliminated via the lungs. In a clinical study that examined SF6 elimination twenty minutes following Lumason injection, the mean cumulative recovery of SF6 in expired air was 82 ± 20% (SD) at the 0.03 mL/kg dose and 88 ± 26% (SD) at the 0.3 mL/kg dose.

4 APPENDICES

4.1 APPLICANT'S PROPOSED PACKAGE INSERT
4.2 OCP FILING FORM

4.1 Applicant's Proposed Package Insert

16 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

4.2 OCP Filing Form

CLINICAL PHARMACOLOGY FILING FORM

Application Information			
NDA/BLA Number	203-684	**SDN**	31
Applicant	Bracco Diagnostics Inc.	**Submission Date**	June 4, 2015
Generic Name	Sulfur hexafluoride lipid-type A microspheres for injectable suspension, for intravenous use	**Brand Name**	LUMASON
Drug Class	Ultrasound Imaging agent		
Indication	Lumason is an ultrasound contrast agent indicated for use: in adult patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border; **and in adult and pediatric patients** [redacted (b) (4)] **characterization of focal liver lesions.** The indication in **red** color is the new indication proposed by the sponsor.		
Dosage Regimen	Echocardiography: Recommended dose after reconstitution is 2 mL administered as an intravenous bolus injection. During a single examination, a second injection of 2 mL may be administered to prolong contrast enhancement. **Ultrasonography of the Liver: Recommended dose after reconstitution is 2.4 mL** [redacted (b) (4)] **administered as an intravenous** [redacted (b) (4)] **injection . During a single examination, a second injection of 2.4 mL** [redacted (b) (4)] **may be administered if** [redacted (b) (4)] **. The indication in red color is the new indication proposed by the sponsor.**		
Dosage Form	Injectable suspension	**Route of Administration**	IV push
OCP Division		**OND Division**	

OCP Review Team	Primary Reviewer(s)	Secondary Reviewer/ Team Leader
Division	Christy S John, Ph.D.	Gene Williams, Ph.D.
Pharmacometrics	N/A	N/A
Genomics	N/A	N/A

Review Classification	☑ Standard ☐ Priority ☐ Expedited		
Filing Date	6/4/2015	**74-Day Letter Date**	8/18/2015
Review Due Date	2/4/2016	**PDUFA Goal Date**	4/4/2016

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

☑ Yes

☐ No

If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

☐ Yes

☑ No

If yes list comment(s)

Is there a need for clinical trial(s) inspection?

☐ Yes

☑ No

If yes explain

Clinical Pharmacology Package			
Tabular Listing of All Human Studies	☑ Yes ☐ No	Clinical Pharmacology Summary	☑ Yes ☐ No
Bioanalytical and Analytical Methods	☐ Yes ☑ No	Labeling	☑ Yes ☐ No

Clinical Pharmacology Studies

Study Type		Count	Comment(s)
In Vitro Studies			
☐ Metabolism Characterization			
☐ Transporter Characterization			
☐ Distribution			
☐ Drug-Drug Interaction			
In Vivo Studies			
Biopharmaceutics			
☐ Absolute Bioavailability			
☐ Relative Bioavailability			
☐ Bioequivalence			
☐ Food Effect			
☐ Other			
Human Pharmacokinetics			
Healthy Subjects	☐ Single Dose		There are no new clinical pharmacology studies included with this submission. All PK studies in support of this NDA were reviewed earlier for the approval of NDA203-684.
	☐ Multiple Dose		
Patients	☐ Single Dose		
	☐ Multiple Dose		
☐ Mass Balance Study			
☐ Other (e.g. dose proportionality)			
Intrinsic Factors			
☐ Race			
☐ Sex			
☐ Geriatrics			
☑ Pediatrics		6	Six publications are submitted in support of pediatric safety, efficacy, and dosing.
☐ Hepatic Impairment			
☐ Renal Impairment			
☐ Genetics			
Extrinsic Factors			

☐ Effects on Primary Drug		
☐ Effects of Primary Drug		
Pharmacodynamics		
☐ Healthy Subjects		
☐ Patients		
Pharmacokinetics/Pharmacodynamics		
☐ Healthy Subjects		
☐ Patients		
☐ QT		
Pharmacometrics		
☐ Population Pharmacokinetics		
☐ Exposure-Efficacy		
☐ Exposure-Safety		

Total Number of Studies	**In Vitro**		**In Vivo**	6
Total Number of Studies to be Reviewed				6

Criteria for Refusal to File (RTF)		
RTF Parameter	**Assessment**	**Comments**
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	☐Yes ☐No ☑N/A	
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	☐Yes ☐No ☑N/A	
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	☐Yes ☐No ☑N/A	There are no new clinical pharmacology studies included with this submission. All PK studies in support of this NDA were reviewed earlier for the approval of NDA203-684.
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	☐Yes ☐No ☑N/A	
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	☐Yes ☐No ☑N/A	
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	☑Yes ☐No ☐N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	☐Yes ☐No ☑N/A	
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	☑Yes ☐No ☐N/A	There are no new clinical pharmacology studies included with this submission. The applicant refers to PK studies submitted to original NDA 203-684.
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks	☑Yes ☐No ☐N/A	

work leading to appropriate sections, reports, and appendices?		
Complete Application **10.** Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	☐Yes ☐No ☑N/A	
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	☐Yes ☐No ☑N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	☐Yes ☐No ☑N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	☐Yes ☐No ☑N/A	
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	☐Yes ☑No ☐N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	☐Yes ☑No ☐N/A	
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	☐Yes ☑No ☐N/A	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	☐Yes ☐No ☑N/A	
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	☑Yes ☐No ☐N/A	
9. Was the translation (of study reports or	☐Yes ☐No ☑N/A	

other study information) from another language needed and provided in this submission?		

Filing Memo
There are no new clinical pharmacology studies included with this submission. The clinical pharmacology issue with this NDA is dose justification for pediatric patients.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHRISTY S JOHN
02/26/2016

GENE M WILLIAMS
02/26/2016
I concur with the recommendations

NAM ATIQUR RAHMAN
02/29/2016
I agree with the Team's recommendation.