

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203684Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA/BLA # **203684** **Lumason (sulfur Hexafluoride lipid type-A microspheres)**
Product Name: _____

PMR/PMC Description: **Deferred pediatric study under PREA: Conduct a multicenter clinical evaluation of safety and efficacy in pediatric patients ages 9-17 years of age of Lumason as a contrast agent in pediatric echocardiography.**

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>10/31/2014</u>
	Study/Trial Completion:	<u>12/31/2017</u>
	Final Report Submission:	<u>05/31/2018</u>
	Other: Blinded Reads	<u>12/31/2017</u>
	Draft Protocol Submitted	<u>02/25/2014</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

**This deferred PREA pediatric study is for ages 9 to 17 years
Adult indication is ready for approval; pediatric studies have not been conducted.**

The Pediatric Research Committee granted a deferral for children less than 9 years of age because Lumason has extremely limited applicability in the less than 9 age group.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Pediatric patients have not been included in clinical trials to date. The goal of this PMR study is to obtain safety and efficacy information in pediatric patients 9-17 years of age. The Sponsor will be evaluating safety and efficacy of Lumason as a contrast agent in pediatric echocardiography.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Evaluation of efficacy of Lumason echocardiography vs. non-contrast echocardiographic imaging for left ventricular endocardial border delineation (EBD) among 92 patients aged 9-17 years (males and females) and safety of Lumason-enhanced echocardiography.

- **Efficacy: Reduction in the proportion of patients with inadequate EBD in ≥ 1 segment, ≥ 2 segments, ≥ 2 adjacent segments, and in at least 1 or 2 critical segments (distal part of main branch coronary artery) could be observed with Lumason.**
- **Safety: Pharmacokinetic assessment of 12 patients enrolled in the study: 6 patients 9-12 years of age (3 males and 3 females) among 6 patients 12-17 years of age (3 males and 3 females).**

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

- Other

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

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/s/

RENE C TYSON
10/10/2014

IRA P KREFTING
10/10/2014

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

Memorandum

****PRE-DECISIONAL AGENCY MEMO****

Date: September 22, 2014

To: Frank Lutterodt
Regulatory Project Manager
Division of Medical Imaging Products (DMIP)

From: Zarna Patel, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: **Lumason (sulfur hexafluoride lipid-type A microspheres) for injectable suspension, for intravenous use**
NDA 203684
OPDP Comments on draft product labeling

OPDP has reviewed the proposed Package Insert (PI) submitted for consult on September 22, 2014, for Lumason (sulfur hexafluoride lipid-type A microspheres) for injectable suspension, for intravenous use. Our comments on the PI are based on the proposed labeling emailed to us on September 22, 2014. OPDP's comments are provided directly on the attached marked-up copy of the proposed PI.

Thank you for the opportunity to comment on the proposed labeling.

If you have any questions, please contact Zarna Patel at 301.796.3822 or zarna.patel@fda.hhs.gov.

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

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/s/

ZARNA PATEL
09/22/2014

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: July 10, 2014

Requesting Office or Division: Division of Medical Imaging Products (DMIP)

Application Type and Number: NDA 203684

Product Name and Strength: Lumason (Sulfur Hexafluoride Lipid Microsphere) Kit for Preparation of Injectable Suspension, 25 mg per vial.

Product Type: Kit for single use

Rx or OTC: Rx

Applicant/Sponsor Name: Bracco Diagnostics

Submission Date: April 11, 2014

OSE RCM #: 2014-851

DMEPA Primary Reviewer: Neil Vora, PharmD, MBA

DMEPA Team Leader: Yelena Maslov, PharmD

DMEPA Associate Director: Lubna Merchant, PharmD, MS

1 REASON FOR REVIEW

This review evaluates the proposed container label, carton labeling and prescribing information as well as product design for Sulfur Hexafluoride Lipid Microsphere Kit for NDA 203684 for areas of vulnerability that could lead to medication errors. After receiving a complete response on November 27, 2013, Bracco resubmitted NDA 203684 on April 11, 2014 for review.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B – N/A
Previous DMEPA Reviews	C
Human Factors Study	D – N/A
ISMP Newsletters	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We identified the following areas of vulnerability to medication errors in the vial labels, kit carton labeling, diluent label, and prescribing information labeling.

We also identified tall man lettering used for the proprietary name on all labeling including carton labeling, kit labeling, vial label, diluent label and patient information labeling.

- **Kit for Preparation of Lumason Labeling for 5 kits**
 1. The contents of all the items included with each kit are not clearly stated on the principal display panel (PDP). Thus, this information should be added to ensure health care providers using the kits are aware what is included.
 2. The current proposed PDP is overcrowded; thus the most important information such as product name and route of administration can be overlooked.

3. “For intravenous use only after reconstitution” should have increased prominence on the PDP to avoid confusion with any other route of administration (e.g., intra-theical) since the dose volume is small.

- **Kit for Preparation of Lumason Labeling for 1 kit**

1. “For intravenous use only after reconstitution” should have increased prominence on the PDP to avoid confusion with any other route of administration (e.g., intra-theical) since the dose volume is small.

- **Vial Label**

1. The diluent’s concentration (i.e., 0.9%) on the vial label is not present, and can be a potential cause for confusion or misinterpretation.
2. Since most of the text on the vial label PDP is bolded, the readability of the most important information is decreased; and thus, can be overlooked.
3. Strength of the Sulfur Hexafluoride Lipid Microsphere is not listed.

- **Diluent Label**

1.  (b) (4)
Thus, a diluent label should be modified to also indicate the contents of the syringe containing the active drug after reconstitution (i.e., sulfur hexafluoride) to avoid misbranding.

- **Prescribing Information**

1. Under the reconstitution instructions, the specific volume of the dose (i.e., 2 mL) should be stated to avoid any ambiguity.

4 CONCLUSION

DMEPA concludes that the proposed labels and labeling can be improved to clarify information, as well as to increase the readability and prominence of important information on the Lumason vial label, diluent label, kit carton labeling for 1 kit and kit carton labeling for 5 kits.

Additionally, the proposed prescribing information labeling can be improved by clarifying information to promote the safe use of the product.

4 RECOMMENDATIONS

4.1 RECOMMENDATIONS FOR THE DIVISION

DMEPA provides the following comments for consideration by the Review Division prior to the approval of this NDA:

A. Prescribing Information, Dosage and Administration, Section 2.2, Reconstitution Steps

1. Current instructions for step 7 state:

“Invert the system and slowly withdraw [REDACTED] ^{(b) (4)} of suspension into the syringe (see Figure 7).”

Revise the instructions for step 7 to state, “Invert the system and slowly withdraw 2 mL of suspension into the syringe (see Figure 7).” We recommend this to minimize dosing errors and avoid ambiguity in dosing of the product since there are no dose modifications for this particular product.

4.2 RECOMMENDATIONS FOR THE BRACCO DIAGNOSTICS

A. Kit for Preparation of Lumason Labeling for 5 kits

1. Currently, the expression of net quantity for the Lumason carton labeling is unclear due to the use of a dash. As a result, we recommend revising the net quantity of the vials by removing the dash or using the word “of.” In addition, we recommend indicating the other contents consisting of 5 mini spikes and 5 sodium chloride prefilled syringe that are included in each kit.

For example,

5 single use Lumason Kits with each kit containing:

1 vial of Lumason for injection, 25 mg/5 ml

1 Sodium Chloride Injection, USP for use with Lumason

1 Mini-Spike

2. Increase the size of the PDP label to allow more space to increase readability as information such as the barcode and manufacturer’s information crowds the principal display panel and important information such as route of administration can be overlooked.

3. Increase prominence of the statement “For intravenous use only after reconstitution” by increasing the font size. We provide this recommendation to ensure route of administration is clearly visible to help prevent medication errors related to wrong route of administration (e.g., intra-theal) since such a small volume will be used in a syringe.

B. Kit for Preparation of Lumason Labeling for 1 kit

1. See Recommendations A.2 and A.3 and revise the Kit labeling for one kit accordingly.

C. Vial Label

1. We recommend revising the sodium chloride statement on the Lumason vial label to exclude the volume of sodium chloride (i.e., 5 mL) needed since the entire syringe should be used. Additionally, use of the volume ‘5 mL’ may produce confusion regarding the correct strength of the product. Instead, we recommend you include the strength and un-bold the statement “**with 5 mL Sodium Chloride Injection, USP**” and revise to the following:

“with Sodium Chloride 0.9% Injection, USP.”

2. Include the strength of the active ingredient, Sulfur Hexafluoride Lipid Microsphere to indicate 25 mg per vial.

D. Diluent Label

1. Step 7 in Section 2.2, of Dosage and Administration section of the PI states to withdraw (b) (4)



We recommend addressing this concern through labelling. For example, you may consider placing a label underneath the current diluent label. The diluent label then would have the capability of being peeled back to reveal the contents of the syringe containing the active ingredient after reconstitution.

E. Tall Man Lettering

1. Presentation of [REDACTED] (b) (4) within the name is unacceptable. [REDACTED] (b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

¹ Cohen, MR. Medication Errors, 2nd ed., American Pharmacists Association, Washington, D.C., 2007, p. 89-90.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Lumason that Bracco Diagnostics submitted on April 25, 2014.

Table 2. Relevant Product Information for Lumason	
Active Ingredient	Sulfur Hexafluoride Microsphere
Indication	Ultrasound contrast agent indicated for use in patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border.
Route of Administration	Intravenous
Dosage Form	Injectable Suspension
Strength	25 mg /5 mL
Dose and Frequency	2 mL (b) (4) administered as an intravenous bolus injection during echocardiography. During a single examination, a second injection of 2 mL may be administered to prolong contrast enhancement.
How Supplied	Kit for preparation of injectable suspension consisting of the following parts: <ol style="list-style-type: none">1. One vial of 25 mg lyophilized powder2. Prefilled syringe of 0.9% Sodium Chloride Injection, USP, diluent3. Mini-Spike
Storage	Store the kit before and after reconstitution at 25°C (77°F); excursions permitted to 15-30°C (59°-86°F)
Container Closure	1 single use kit per cart and 5 single use kits per carton

APPENDIX B. NOT APPLICABLE

C. PREVIOUS DMEPA REVIEWS

C.1 Methods

We searched the L:Drive on May 29, 2014 using the terms, “sulfur hexafluoride lipid microsphere” to identify reviews previously performed by DMEPA.

C.2 Results

A proprietary name review was conducted in OSE Review # 2013-2105 for NDA 203684 on October 31, 2013, and the name was approved.

A label and labeling review was conducted in OSE Review # 2012-439 for NDA 203684 on August 8, 2012, and the label was tentatively approved based on recommended changes.

APPENDIX D. NOT APPLICABLE

APPENDIX E. NOT APPLICABLE

APPENDIX F. NOT APPLICABLE

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,² along with postmarket medication error data, we reviewed the following Lumason labels and labeling submitted by Bracco Diagnostics on April 25, 2014.

- Carton labeling (Appendix G.2.1)
- Kit Labeling (Appendix G.2.2)
- Vial Label (Appendix G.2.3)
- Diluent Label (Appendix G.2.4)
- Full Prescribing Information (No Image)

² Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

NEIL H VORA
07/10/2014

YELENA L MASLOV
07/10/2014

LUBNA A MERCHANT
07/10/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES

MEMORANDUM

Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
White Oak Building 66
10903 New Hampshire Avenue
Silver Spring, MD 20993

Date: March 5, 2014

From: Mary Brooks, CDR USPHS, MS, BSN, RN, Nurse Consultant, WO66, RM 2524
CDRH/ODE/DAGRID/General Hospital Devices Branch (GHDB)

To: Frank Lutterodt, M.S., Regulatory Health Project Manager, Division of Medical
Imaging Products Office of Drug Evaluation IV

Subject: CDRH Consult Review Additional Information – NDA 203-684

The Center for Drug Evaluation and Research (CDER)] has requested a consult from the Center for Devices and Radiological Health (CDRH, regarding NDA 203-684 to review additional information request responses from sponsor related the combination product device constituent.



a.

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/s/

FRANK A LUTTERODT

03/07/2014

Follow-up Consult Review checked in on behalf of CDRH Reviewer: Mary E. Brooks RN, BSN, MS
Commander, United States Public Health Service Nurse Consultant Division of Anesthesiology,
General Hospital, Respiratory Infection Control, & Dental Devices Office of Device Evaluation
Center for Devices & Radiological Health

DEPARTMENT OF HEALTH AND HUMAN SERVICES

MEMORANDUM

Food and Drug Administration
Office of Device Evaluation
10903 New Hampshire Avenue
Silver Spring, MD 20993

Date: July 22, 2013
From: CDR Mary Brooks, RN, BSN, MS
DAGID/GHDB, WO66-G456
Submission: ICC 1300254 – GEN1300371
NDA 203684

This consult is based on deficiency questions identified in previous consult from September 2012.

Deficiency 2. Your drug is to be supplied within a package that contains the drug vial, a pre-filled glass syringe (b) (4) and a transfer device (to attach the pre-filled syringe to the drug vial). The transfer device is referred to as the “Mini-Spike (b) (4) Your application contained a letter of authorization from B. Braun Melsungen AG, the manufacturer of the Mini-Spike (b) (4) This letter authorized FDA to examine 510(k) number (b) (4) in support of the Mini-Spike (b) (4) We examined this 510(k) application and determined the model known as Mini-Spike (b) (4) is not part of (b) (4) submission clearance. We have determined that Mini-Spike (b) (4) is a model number available in the European market and not available for distribution within the USA.

Deficiency 2a. Provide a document that describes the fundamental differences between the Mini-Spike (b) (4) model and the other transfer device models cleared under (b) (4) Include sufficient information to allow us to verify the quality, composition and construct of the Mini-Spike (b) (4)

2a. Bracco Response:

Bracco has had discussions with B. Braun regarding the Mini-Spike (b) (4) and concurs with FDA’s statement regarding the transfer device. Therefore, Bracco hereby informs the agency that, with this submission in response to FDA’s Complete Response Letter of 19th October 2012, the company has deleted the Mini-Spike (b) (4) from this NDA. Bracco intends to provide the “Mini-Spike” (cleared for marketing under (b) (4)) as part of the product kit to be supplied following approval of NDA 203-684.

(b) (4)

In the original NDA, data were provided which demonstrated that different reconstitution techniques had no impact upon the microsphere suspension (M3.2.P.2.2 pages 8-12).

Comparison of the characteristics of the suspension after reconstitution using the Mini-Spike (b) (4) and Mini-Spike showed no difference between the two.

As a further point of clarification, the trade name identified in (b) (4) is “(b) (4) Mini-Spike (b) (4) but the device cleared under (b) (4) is also marketed in the US under the trade name “Mini-Spike”, which is (b) (4) in the B.Braun product catalogue. Accordingly, Bracco provides herein a [new Letter of Authorization](#) from B. Braun Melsungen AG which

authorizes the agency to access the information in (b) (4) regarding the Mini-Spike device, which is now included in Bracco's NDA in M1.4.1.

FDA Response: Acceptable

Review of (b) (4) Mini-Spike, was completed in a previous consult to CDER. (b) (4) is cleared with the indications for, (b) (4)

(b) (4) Ordinarily this is an acceptable device for use with vial medications however, this NDA 203684 drug produces sulfur hexafluoride micro bubbles. This is some concern based on response to FDA deficiency 2b that the sponsor is XXXX

Deficiency 2b. Within your response, describe any (b) (4) within the Mini-Spike (b) (4) Specifically, does the device contain (b) (4)

2b. Bracco Response:

As noted above in Bracco's response to deficiency 2a, with this this submission in response to FDA's Complete Response Letter of 19th October 2012, the company has deleted the Mini-Spike (b) (4) from this NDA. Instead, Bracco has included the "Mini-Spike" (cleared for marketing under (b) (4)) in this NDA. The Mini-Spike (b) (4) for (b) (4) injecting and withdrawing fluid from the vial. (b) (4)

FDA Response: Additional Information Request

Upon review of (b) (4) submission, attachment 4 design specification, (b) (4)

1) (b) (4)

Deficiency 2c. Please notify the device manufacturer, B. Braun Melsungen AG to contact CDRH's Office of Device Evaluation, LCDR Mary Brooks (301) 796-6078, to discuss the regulatory pathway necessary for the Mini-Spike (b) (4) model to receive 510(k) clearance.

2c. Bracco Response:

As noted above in Bracco's response to deficiency 2a, with this submission in response to FDA's Complete Response Letter of 19th October 2012, the company has deleted the Mini-Spike (b) (4) from this NDA. Instead, Bracco has included the "Mini-Spike" (cleared for marketing under (b) (4)) in this NDA. Therefore, there is no need for Bracco to notify for B. Braun Melsungen AG to contact CDRH's Office of Device Evaluation to discuss the Mini-Spike (b) (4) model since it has been deleted from this NDA and will not be marketed in the United States.

The relevant sections of Module 3 and the Quality Overall Summary in Module 2 have been updated to reflect the change in the spike and the revised letter of authorization from B.Braun.

FDA Response: Acceptable

Deficiency 3.

The (b) (4) does not have a reference premarket 510(k) clearance number. Please clarify whether or not the device has a 510(k) clearance. If the device is to be reviewed under the NDA, the following information will be necessary to complete the review:

- a. A list of raw materials, to include the Material Safety Data Sheets (MSDS),
- b. The design specifications,
- c. A biocompatibility assessment of the final finished product (after sterilization). Please refer to ISO 10993-1, Biological evaluation of medical devices — Part 1: Evaluation and testing.
- d. Performance testing as outlined in ISO 594-2, (b) (4)

Bracco Response:

The (b) (4) that attaches to the glass syringe has no 510(k) clearance. Instead, the device is to be reviewed under the NDA.

(b) (4) has submitted DMF No. (b) (4) Type III for the (b) (4), a letter authorizing FDA to access this DMF for the purpose of review of NDA 203-684 is included in the revised Module 1 section 1.4.1 of this submission in response to FDA's Complete Response Letter of 19th October 2012.

Also, section of M3.2.P.7 and the [Quality Overall Summary in Module 2](#) have been updated include reference to the letter of authorisation from (b) (4)

Deficiency 3a. A list of materials, to include the Material Safety Data Sheets (MSDS)

3a. Bracco Response:

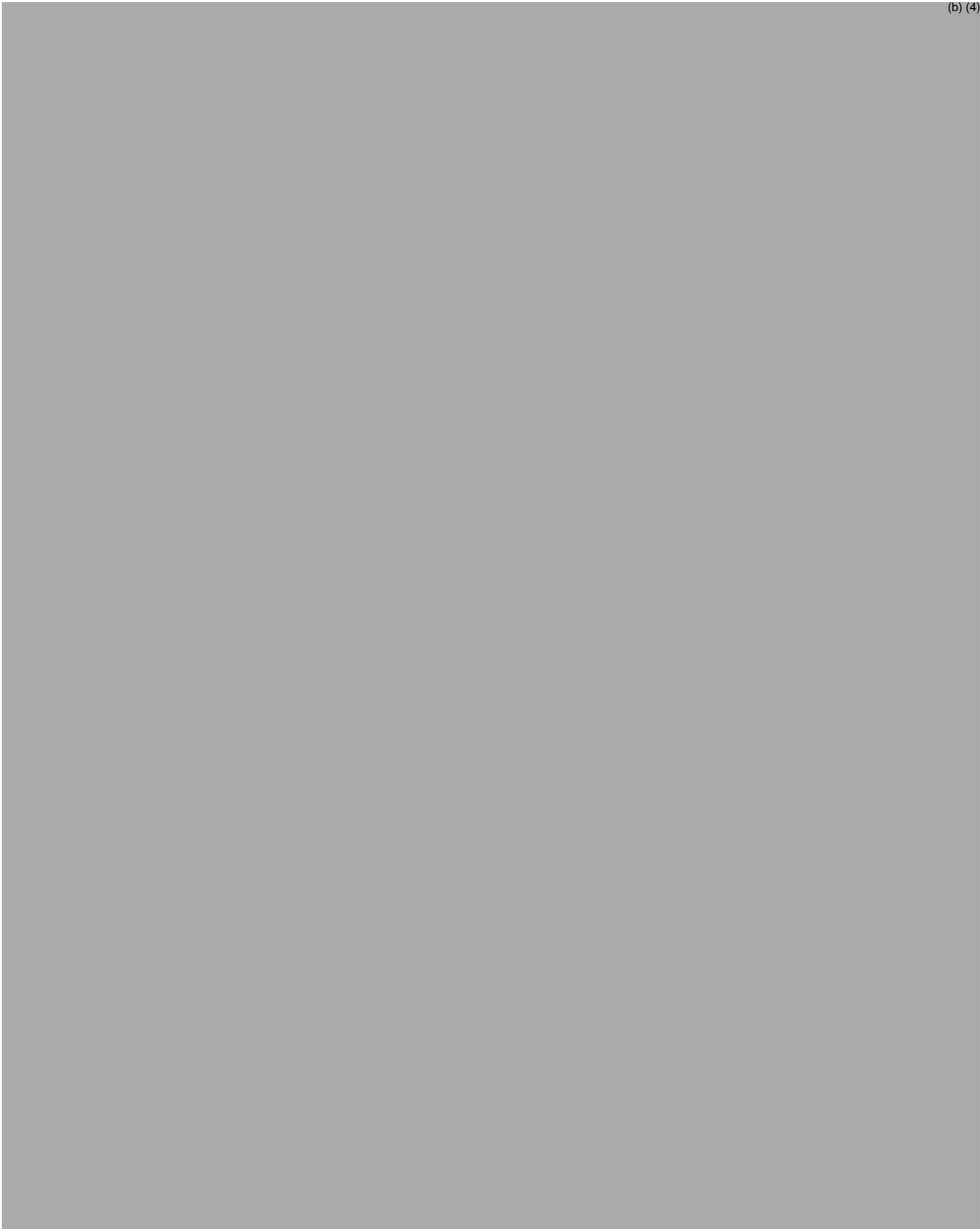
(b) (4)

Table 1: List of Materials

(b) (4)

(b) (4)

(b) (4)



FDA Response: Acceptable

Conclusion:

The sponsor has addressed CDRH's concerns related to device performance between the syringe barrel, (b) (4) and the Mini-Spike. However the sponsor stated the Mini-Spike does not have (b) (4) The question below should be asked of the sponsor.

- 1) Our records indicate the Mini-Spike (b) (4)

Digital Signature Concurrence Table

Reviewer Sign-Off	
Branch Chief Sign-Off (optional)	

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/s/

FRANK A LUTTERODT

03/07/2014

Follow-up Consult Review checked in on behalf of CDRH Reviewer: Mary E. Brooks RN, BSN, MS
Commander, United States Public Health Service Nurse Consultant Division of Anesthesiology,
General Hospital, Respiratory Infection Control, & Dental Devices Office of Device Evaluation
Center for Devices & Radiological Health

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: October 15, 2013

To: Frank Lutterodt
Regulatory Project Manager
Division of Medical Imaging Products(DMIP)

From: Emily Baker, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: **NDA 203684**
OPDP Labeling Comments for (b) (4) (Sulfur Hexafluoride Microbubbles)

OPDP has reviewed the proposed Package Insert (PI) submitted for consult on July 2, 2013, for (b) (4) (Sulfur Hexafluoride Microbubbles). Our comments on the PI are based on the proposed labeling emailed to us on October 2, 2013. OPDP's comments are provided directly on the attached marked-up copy of the proposed PI.

Thank you for the opportunity to comment on the proposed material.

If you have any questions, please contact Emily Baker at 301.796.7524 or Emily.Baker@fda.hhs.gov.

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/s/

EMILY K BAKER
10/15/2013



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs - Immediate Office
Pediatric and Maternal Health Staff
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9855

MEMORANDUM TO FILE

Date: October 2, 2013

From: Ethan D. Hausman, MD, Medical Officer
Pediatric and Maternal Health Staff (PMHS), OND

Through: Hari Cheryl Sachs, MD, Medical Team Leader
PMHS, OND
Lynne P. Yao, MD, OND Associate Director
PMHS

NDA Number: 203684

Sponsor: Bracco Diagnostics, Inc.

Drug: SonoVue (sulfur hexafluoride) Microbubbles

Dosage form and route of administration: Lyophilized powder for reconstitution and intravenous (IV) injection

Proposed Pediatric dosing regimen: [REDACTED] (b) (4)

Propose Indication: For use in echocardiography (ECHO) in patients with suboptimal ECHO, to obtain left ventricular opacification and improve endocardial border delineation (EBD)

Division Consult Request: The Division of Medical Imaging Products (DMIP) requested that PMHS review and comment on the sponsor's pediatric development plan (PDP) which includes a proposed study in children 9 to 17 years of age, and a request for partial waiver for children younger than 9 years old.

Background

SonoVue (sulfur hexafluoride, SF-6) is intended for use as an echocardiographic (ECHO) imaging agent for patients with suboptimal echocardiograms to obtain left ventricular opacification and improve endocardial border delineation (EBD).

The NDA received a Complete Response (CR) Letter on October 19, 2012 due to facility inspection deficiencies. The sponsor (applicant) resubmitted the NDA for consideration of approval in May 2013.



In the current re-submission, the applicant submits a pediatric development plan with a proposed study for pediatric patients 9 through 17 years of age and a request for a partial waiver in pediatric patients younger than 9 years of age. The applicant's proposed timeline is summarized in Table 1 below.

Table 1: Timeline for SonoVue Pediatric Development Plan (from page 20 of the sponsor's proposed Pediatric Development Plan).

Proposed Action	Tentative Timeline
(b) (4)	

Drug Background

According to draft labeling from May 2013, SF-6 microspheres have lower acoustic impedance than non-aqueous tissue and this characteristic allows visualization of the density difference between blood (with dissolved SF-6) and the surrounding tissues. The compound has approximately 40 to 50% first pass elimination in the pulmonary

¹ McMahon C, Ayres N, Bezold L, et al. Safety and efficacy of intravenous contrast imaging in pediatric Echocardiography. *Pediatr Cardiol.* 2005 Jul-Aug;26(4):413-417.

circulation, with 82% elimination of a 0.3 mL/kg dose at 20 minutes and 88% elimination of a 0.3 mL/kg dose 20 minutes.²

Proposed Study in 9 to 17 year old Children

A complete protocol has not been submitted. The protocol synopsis is summarized below.

(b) (4)

The study will enroll approximately 92 male and female patients (b) (4) Key endpoints are pharmacokinetics (PK) and the change from baseline in total of left ventricular (LV) EBD score (i.e., patients are their own controls). Blood for pharmacokinetic (PK) assessment will be collected on 6 patients from 9 to 12 years old and on another 6 patients from >12 through 17 years of age. (b) (4)

(b) (4) the proposed clinical study is designed to establish PK, safety, and efficacy.

Reviewer comment: Overall study design and extrapolation are addressed in this comment. Other specific elements, such as dose, are addressed later in this document.

The study design appears generally consistent with adult studies of other contrast agents such as Gadavist. (b) (4)

(b) (4)

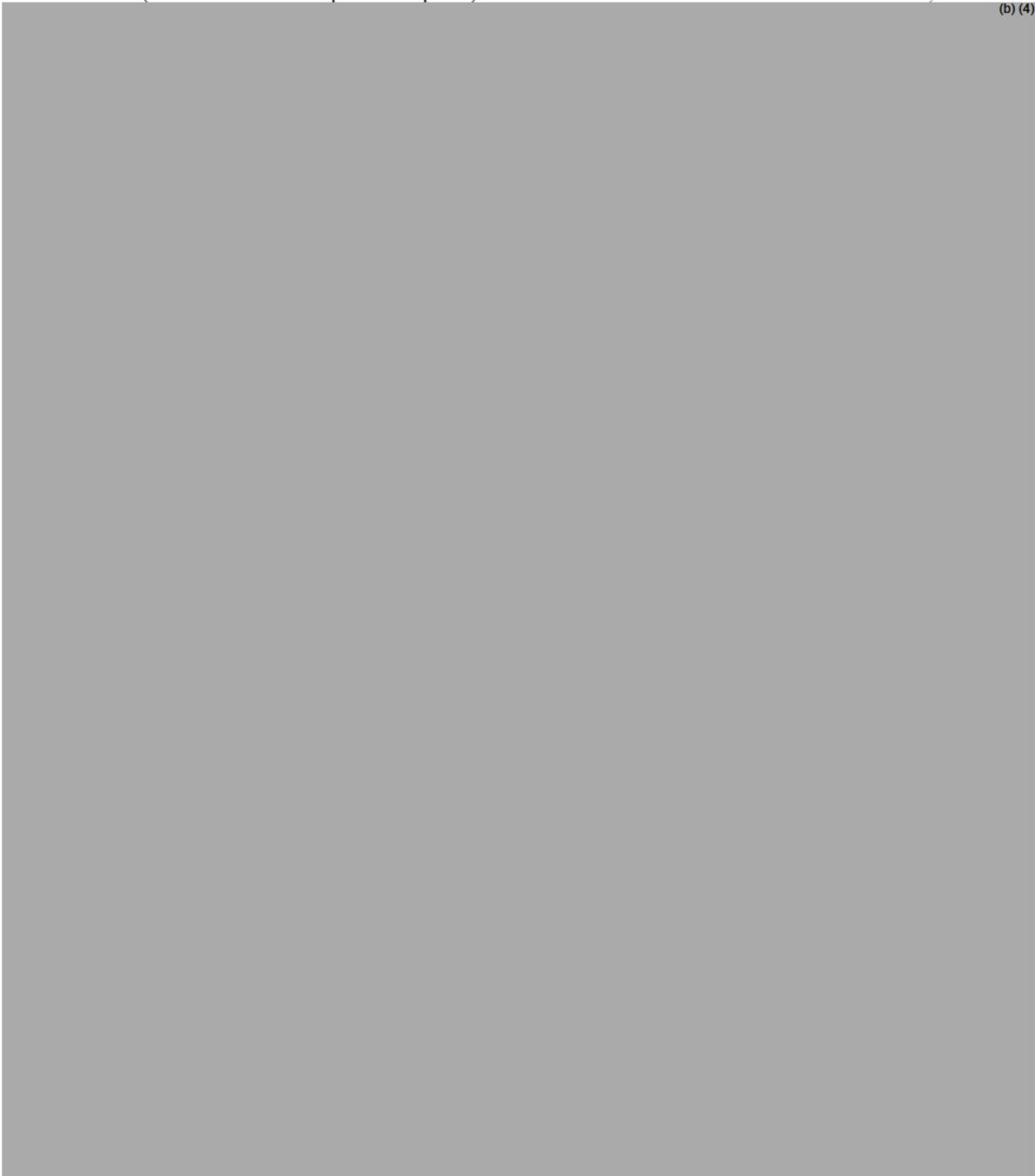
(b) (4)

Proposed Dose and Dose Formulation

(b) (4)

(b) (4)

⁴ Snyder W, Cook M, Karhausen L, et al. Report of the task group on reference man. IRCP Publication 23. A report prepared by a task group of Committee 2 of IRCP. Oxford Press. 1975 (revised 1980).



Request for a partial waiver in patients younger than 9 years of age

The sponsor's rationale for waiving studies in children younger than 9 years of age is based on impracticability of study due to the scarcity of patients likely to benefit from contrast enhanced EBD in that age group.⁷ (b) (4)

⁷ McMahon. Op. cit.

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Conclusion and Recommendations:

Study in 9 to 17 year old patients

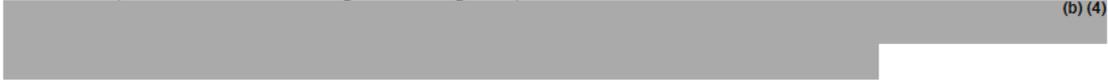
The sponsor's proposed study of patients 9 to 17 years of age with suboptimal ECHO to obtain left ventricular opacification and improve EBD is generally acceptable; however, DMIP should address the following issues:

1. PMHS recommends that DMIP inform the sponsor that their pediatric development plan may employ partial extrapolation (b) (4)
2. PMHS recommends that CMC review and comment on the rationale for not requiring separate pediatric formulation(s) for patients ages 9 to 17, (b) (4)
3. PMHS recommends that CMC and Pharmacotoxicology review and comment on any pediatric implications of excipients at the concentrations used (for example PEG4000 and palmitic acid) whether the 'microbubbles' in the reconstituted product present unique pediatric safety concerns.
4. PMHS recommends that the rationale for the proposed dose and justification be reviewed by Clinical Pharmacology and Pharmaco-Toxicology.
5. The maximum dose in children in the proposed study should not exceed the maximum dose in adult clinical trials (2.0 mL).
6. The enrollment criteria for the proposed study in 9 to 17 year old patients appear acceptable; however, acceptance of the enrollment criteria is deferred to DMIP.
7. The proposed efficacy endpoint appears appropriate; however, acceptance of the efficacy endpoint and safety assessments is deferred to DMIP's review of the protocol which has not yet been submitted.
8. PMHS recommends that Clinical Pharmacology review and comment on the PK monitoring plan.
9. DMIP should be satisfied that the proposed safety monitoring plan is adequate. Additionally, since draft labeling states that serious cardiopulmonary reactions, including fatalities, may occur during or shortly following the injection of ultrasound contrast agents, including SF-6, DMIP should consider whether a monitoring period and access to resuscitation paraphernalia should be required.
10. The protocol synopsis should include a specific list of laboratory assessments.
11. DMIP and Statistics should be satisfied that the proposed study size. Statistics should comment on the statistical analysis plan.

Request for Partial waiver of studies in patients younger than 9 years old

(b) (4)

Additional comment:



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/s/

ETHAN D HAUSMAN
10/02/2013

HARI C SACHS
10/02/2013
I agree with these recommendations.

LYNNE P YAO
10/08/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling and Packaging Review

Date: August 15, 2013

Reviewer: Yelena Maslov, Pharm.D., Team Leader
Division of Medication Error Prevention and Analysis

Drug Name and Strength: (b) (4) (Sulfur Hexafluoride Lipid Microsphere)
Kit for Preparation of Injectable Suspension,
25 mg/vial

Application Type/Number: NDA 203684

Applicant/sponsor: Bracco Diagnostics, Inc.

OSE RCM #: 2013-1349

*** This document contains proprietary and confidential information that should not be released to the public.***

1 INTRODUCTION

This review evaluates the revised container label and carton labeling for Sulfur Hexafluoride Lipid Microsphere Kit for Preparation of Injectable Suspension, NDA 203684, submitted in Applicant's Resubmission on May 31, 2013 after a Complete Response. The Applicant submitted labels and labeling in response to DMEPA's previous comments to the Applicant in OSE Review #2012-439, dated August 8, 2012.

2 MATERIAL REVIEWED

The revised container label and carton labeling submitted to the FDA on May 31, 2013 (See Appendix A) and OSE Review #2012-439, dated August 8, 2012, were evaluated to assess whether the revisions adequately address our concerns from a medication error perspective.

3 CONCLUSIONS AND RECOMMENDATIONS

The revised container labels and carton labeling submitted on May 31, 2013, address all of DMEPA's concerns. However, we have one additional recommendation regarding deletion of the proprietary name, Sonovue, since it was found unacceptable on September 17, 2012. Please see this recommendation below:

Vial Label, Syringe Label, Carton Labeling, Shipper Labeling:

1. Remove the proprietary name, Sonovue, from the labels and labeling as this name was found unacceptable.

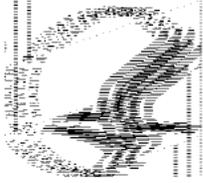
If you have further questions or need clarifications, please contact Sandra Rimmel, project manager, at 301-796-2445.

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/s/

YELENA L MASLOV
08/15/2013



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

MEMORANDUM TO FILE

Date: May 30, 2013

From: Jeanine Best, MSN, RN, PNP, Senior Clinical Analyst
Pediatric and Maternal Health Staff

Through: Hari Cheryl Sachs, MD, Team Leader – Pediatrics
Pediatric and Maternal Health Staff

Lynne P. Yao, MD, OND Associate Director,
Pediatric and Maternal Health Staff

To: Division of Medical Imaging Products (DMIP)

Applicant: Bracco Diagnostics, Inc.

Drug: SonoVue (sulfur hexafluoride microbubbles) injection,

NDA: 203684

Route of Administration: Intravenous

Drug Class: Ultrasound Contrast Agent

Indication: for use in echocardiography in patients with suboptimal echocardiograms to obtain left ventricular opacification and improve endocardial border delineation

Subject: Type C Meeting to discuss proposed Pediatric Plan

Internal Meeting: May 16, 2013

Applicant Teleconference: May 20, 2013

Consult Question: Please attend internal and applicant meetings to discuss the applicant's proposed Pediatric Plan.

INTRODUCTION and BACKGROUND

On April 23, 2013, Bracco Diagnostics, Inc. submitted a Meeting Background Package for their May 20, 2013, Type C Teleconference scheduled to discuss their proposed Pediatric Plan for SonoVue (sulfur hexafluoride microbubbles) injection.

The Division of Medical Imaging Products (DMIP) consulted the Pediatric and Maternal Health Staff (PMHS) to attend internal and applicant meetings to discuss the applicant's proposed Pediatric Plan for SonoVue.

On October 19, 2012, Bracco Diagnostics, Inc. was issued a Complete Response Letter for SonoVue (sulfur hexafluoride microbubbles) injection due to facility inspection deficiencies. SonoVue is an ultrasound contrast agent intended to provide contrast enhancement of the endocardial borders during echocardiography in patients with suboptimal echocardiograms. Factors that affect suboptimal echocardiograms in adult patients include obesity and chronic obstructive pulmonary disease. The ultrasound waves that are scattered and reflected at the microbubble-blood interface are visualized in the ultrasound image and result in an increased contrast between the blood and the surrounding tissues. The active component in SonoVue, SF₆, is eliminated via the lungs. In clinical pharmacology studies at 11 minutes post-dose, approximately 80-90% of the SF₆ content was eliminated.¹

The applicant submitted studies in adults to support an indication for use in echocardiography in adult patients with suboptimal echocardiograms to obtain left ventricular opacification and improve endocardial border delineation. (b) (4)

[Redacted text block]

DMIP suggested that the applicant should explore the feasibility of conducting studies in the pediatric population and request waivers in pediatric populations in which studies would be impossible or highly impracticable or use of the drug would be ineffective or potentially unsafe. (b) (4)

[Redacted text block]

¹ See draft labeling, submitted December 20, 2011

Applicant Questions and FDA Preliminary Responses

The following two questions and preliminary responses were discussed at an internal meeting between DMIP and PMHS. The preliminary responses were sent to the applicant on May 17, 2013.

1. Bracco received [REDACTED] (b) (4) a request for a new Pediatric Plan for SonoVue. Bracco has provided to the Division our proposed new Pediatric Plan for review.

Does the Division concur with the plan including the proposed timelines?

FDA Response:

- You need to submit a complete pediatric plan for review. A pediatric plan is a statement of intent that outlines the pediatric studies (e.g., pharmacokinetics, pharmacodynamics, safety, and efficacy) that the sponsor proposes to conduct. The plan should also address the development of an age-appropriate formulation, if applicable, and additional nonclinical studies (e.g., juvenile animal toxicity studies, if applicable). Furthermore, the plan should address whether, and if so on what grounds, the applicant proposes to request a waiver or deferral under PREA. The pediatric plan must address the entire pediatric population (see B. below). Pediatric plans must be reviewed by the Pediatric Review Committee (PeRC). The guidance for pediatric plan may be found at: <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM077855.pdf>
- You propose studying pediatric patients [REDACTED] (b) (4)
[REDACTED]
[REDACTED] Please be aware that dosing, safety, and efficacy must be addressed for all proposed pediatric age groups. We recommend that you provide an adequate justification for including or excluding any pediatric populations as part of your pediatric plan. This justification should also summarize data on the use of SonoVue for echocardiography in pediatric patients [REDACTED] (b) (4) especially use in the situation where the patients had suboptimal echocardiograms and they received the contrast to obtain left ventricular opacification and to improve endocardial border delineation.
- [REDACTED] (b) (4)
[REDACTED]
- Please confirm that pediatric patients who have sufficient echocardiogram visualization without use of a contrast agent will not be enrolled in any proposed clinical study.

2. As part of Bracco's proposed Pediatric Plan the intention is to run a clinical study in a pediatric patient population as a post-approval commitment. Therefore, Bracco has provided a draft clinical protocol for the Divisions review. Does the Division concur with the proposed study design?

FDA Response:

See FDA Response to Question 1. It is premature to comment on the proposed study design prior to FDA agreement regarding your pediatric plan. As stated above, you will need to first submit a pediatric plan for review by the PeRC. After you receive our comments on the pediatric plan, you may develop and submit a final clinical study protocol. You may submit your pediatric plan before or together with your response to the New Drug Application Complete Response letter.

PMHS Summary

PMHS participated and provided responses to the applicant's questions in an internal meeting with DMIP on May 16, 2013 and the applicant teleconference on May 20, 2013. The applicant plans to submit a complete pediatric plan with their Complete Response Submission, anticipated to be submitted in June 2013. All waivers and deferrals will need to be justified and supported with available data. [REDACTED] (b) (4)

[REDACTED] PMHS also recommended to DMIP that a Written Request could be considered [REDACTED] (b) (4)

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/s/

JEANINE A BEST
05/30/2013

LYNNE P YAO
05/31/2013



Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: August 22, 2012

From: CDER DCRP QT Interdisciplinary Review Team

Through: Norman Stockbridge, M.D., Ph.D.
Division Director
Division of Cardiovascular and Renal Products /CDER

To: Frank Lutterodt, RPM
DMIP

Subject: QT-IRT Consult to NDA 203684

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated June 19, 2012 regarding NDA 203684. The QT-IRT received and reviewed the following materials:

- Your consult
- Proposed Label
- Summary of Clinical Safety
- Highlights of Clinical Pharmacology Table
- Investigator's Brochure (November 2011)

QT-IRT Comments for DMIP

We do not consider that a TQT study for SonoVue is needed. SonoVue will be given once and its systemic exposure is limited. The initial elimination is rapid (approximately 75% of the dose is eliminated by 11 minutes post-dose) and the terminal half life is 10 minutes. Since we have not performed a formal review of the ECG data proposed in the label we defer label revision to the review division.

SPONSOR'S PROPOSED LABEL

(b) (4)

BACKGROUND

The review division is asking for our review and comment on whether this NDA supports section 5.6 of the proposed package insert for SonoVue.

SonoVue (Sulfur hexafluoride microbubble) is formulated as a 25 mg sterile lyophilized powder in a (b) (4)-sealed vial. The gas phase in the vial is SF₆. After dispersion in 5 mL of sodium chloride injection, USP (0.9% w/v), 1 mL of the dispersion contains 8μL SF₆ in microbubble, equivalent to 45 μg. SonoVue makes use of stabilized microbubbles of SF₆, a poorly soluble, inert, and totally innocuous gas. SonoVue is isotonic in human plasma and less viscous than blood. It does not contain protein-based materials.

The lyophilized powder is made of a combination of pharmaceutical grade polyethylene glycol (PEG) 4000, phospholipids and palmitic acid. Phospholipids (b) (4)

In SonoVue a mixture of distearoylphosphatidylcholine and dipalmitoyl phosphatidylglycerol sodium is used.

The proposed indication is for use in echocardiography in patients with suboptimal echocardiograms to obtain left ventricular opacification and improve endocardial border delineation. The recommended dose is 2mL administered as an intravenous bolus injection

during echocardiography. During a single examination, a second injection of 2 mL may be administered when deemed necessary.

MARKETING EXPERIENCE

SonoVue has been approved in 27 EU countries under the centralized procedure. Of the 27 countries, 15 were granted marketing authorization of sulphur hexafluoride microbubbles under the trade name of SonoVue on 26 March 2001 by the Commission of the European Communities, and is registered in the other 12 EU countries (Cyprus, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Malta, Poland, Slovakia, Slovenia, Bulgaria, and Romania) who joined the EU. In addition, Norway and Iceland have granted a national authorization corresponding to the Commission Decision issued on 26 March 2001. Iceland implemented it on 08 June 2006. Outside of the EU, SonoVue has been registered in Switzerland, China, Singapore, Hong Kong, South Korea, Canada, and India. SonoVue is marketed for sale in 25 of these 36 countries. (b) (4)

NON-CLINICAL EXPERIENCE

-Effect of SonoVue on ECG at multiples of human dose

A study entitled: “SonoVue: Effects on arterial blood pressure, heart rate, activity and ECG, following intravenous administration (bolus) in the conscious cynomolgus monkey monitored by telemetry” examined the effects of SonoVue on clinical signs, arterial blood pressure, heart rate, locomotor activity, parameters of the ECG (RR, PR, QT, corrected QT and QRS complex duration) and body temperature in the conscious cynomolgus male and female monkey monitored by telemetry. SonoVue was administered at dose levels of 1, 2 or 5 mL/kg or saline at 5 mL/kg. Measurements were carried out over a period of 8 hours post-administration. No clinical signs were observed following the administration of SonoVue (1, 2 or 5 mL/kg) and the analysis of the data showed that under the experimental conditions SonoVue has no relevant effect on blood pressure (mean, diastolic and systolic) or heart rate. In the groups treated with SonoVue, the RR, PR, QRS, QT, and the QTc intervals calculated using the Fridericia and the Bazett formulae, were not different from those observed in the saline control group. It is concluded that SonoVue at doses up to 5 mL/kg administered by intravenous bolus was considered to have no deleterious effects on the cardiovascular functions and on body temperature.

-Animal model with compromised pulmonary function

A study, entitled “A rising dose cardiovascular assessment of intravenously administered SonoVue in an acute model of pulmonary hypertension in anesthetized dogs” has been conducted. Pulmonary arterial hypertension (PAH) was induced by the injection of glass beads (150 to 200 µm) into the right ventricle of the heart. In dogs with induced PAH, cumulative doses of SonoVue (0.1, 0.3 and 1 mL/kg) administered at 15-minute intervals had no effects on arterial blood pressure, heart rate and on QT and QTc (Fridericia’s formula) intervals of the ECG. Furthermore, increasing doses of SonoVue did not modify the myocardial (LV pressure and myocardial contractility) or the pulmonary (tidal volume and respiratory rate) functions. At

the highest dose (1 mL/kg) of SonoVue only, a transient increase (2.5 ± 1.3 mmHg, n=4) in pulmonary arterial pressure (PAP) was observed between 5 to 7 minutes after the administration, this effect was more marked in 1 out of the 4 animals tested.

In addition, a review of the microscopic finding of the toxicology studies did not indicate a pulmonary safety concern at high multiples of human exposure.

CLINICAL INFORMATION

From ISS, Prospective Clinical Trials of Continuous ECG Monitoring (ISS page 95)

Study BR1-112: A single-blind, placebo-controlled, randomized, three-way crossover study designed to acquire and evaluate ECG data in volunteer subjects with CAD. Each subject received SonoVue 0.1 mL/kg, SonoVue 0.5 mL/kg, and placebo according to one of six randomization sequences. a confirmatory prospective 3-way crossover study of intravenous administration of placebo and 2 doses of SonoVue (0.1 mL/kg and 0.5 mL/kg) performed in 49 subjects with documented CAD, showed that the effect of SonoVue on ventricular repolarization and, in general, on cardiac electrophysiology is comparable with placebo. The primary analysis (n=48) of maximum mean increase from baseline in the individualized QTc (QTcI) values confirmed that there was no significant difference between placebo and SonoVue. No dose or time dependency to investigational product administration existed (with respect to mean QTcI intervals at baseline). At the maximum postdose measurement and the mean maximum increase from baseline, the QTcI values were comparable (placebo: 18.4 msec, SonoVue 0.1 mL/kg: 16.8 msec, and SonoVue 0.5 mL/kg: 17.5 msec).

Table 1: Analysis of Maximum Increase From Baseline in QTcI Interval (ms) Within 1 Hour Postdose, Primary Analysis Population in Study BR1-112

Parameter	Placebo (N=48)	SonoVue 0.1 mL/kg (N=48)	SonoVue 0.5 mL/kg (N=48)
Baseline ^a			
Mean (SD)	404.6 (22.7)	403.9 (24.5)	401.8 (23.0)
Median	404.5	399.0	401.0
Range (Min—Max)	362–456	366–465	360–451
Maximum Postdose Value ^b			
Mean (SD)	422.9 (21.9)	420.7 (26.4)	419.3 (23.0)
Median	420.5	414.0	417.0
Range (Min—Max)	385–475	373–486	377–468
Maximum Increase From Baseline ^c			
LS Mean Change (SE)	18.4 (1.3)	16.8 (1.3)	17.5 (1.3)
95% CI for LS Mean Change	(15.9, 20.8)	(14.3, 19.2)	(15.0, 20.0)
SonoVue – Placebo			
Difference in LS Mean Change (SE)		-1.60 (1.60)	-0.85 (1.60)
95% CI for Difference of LS Mean Change		(-4.79, 1.58)	(-4.04, 2.33)
SonoVue 0.5 mL/kg – SonoVue 0.1 mL/kg			
Difference in LS Mean Change (SE)			0.75 (1.60)
95% CI for Difference of LS Mean Change			(-2.43, 3.93)
^a Baseline is the mean of all technically adequate recorded values from 3 hours predose to immediately predose. ^b Postdose value from +1 minute to +1 hour where the maximum increase from baseline occurred. ^c Based on an ANOVA model including dose and period as fixed effects and subject as random effect. QTc Interval Normal Range: 320 - 440 msec QTcI = Individual subject corrected QT interval; SD = Standard deviation; SE = Standard error; LS = Least squares; CI = Confidence interval; Min = minimum; Max = maximum Table data derived from <i>Clinical Trial Report BR1-112</i> .			

Source: ISS, Table SS

Study BR1-113: a prospective, 4-way crossover study was performed to evaluate cardiac electrophysiology data in 53 CAD patient volunteers who were randomized to receive 4 intravenous treatments (i.e., SonoVue 0.1 mL/kg at mechanical index 0.4, SonoVue 0.1 mL/kg at mechanical index 1.5, placebo 0.1 mL/kg at mechanical index 0.4, and placebo 0.1 mL/kg at mechanical index 1.5) according to 1 of 4 sequences. The results of this study demonstrate that SonoVue was not associated with an increased risk of prolonged cardiac repolarization, and was safe and well tolerated regardless of insonation regimen during echocardiography.

Analysis of the maximum increase from baseline in QTcI interval was performed for subjects who had QTcI data at baseline and at least one technically adequate measurement within 1 hour postdose after each treatment. A linear model for a 4-period crossover design was used in the assessment of the primary hypothesis. Subject, treatment, and period were terms in the model. A 2-sided confidence interval for the difference between SonoVue and placebo for each MI level was constructed using the SE obtained from the linear model.

A total of 50 subjects were included in the primary analysis population, i.e., all subjects who had QTcI data at baseline and at least one technically adequate measurement within 1 hour postdose after each of the four treatments (SonoVue 0.1 mL/kg at mechanical index 0.4, SonoVue 0.1 mL/kg at mechanical index 1.5, placebo 0.1 mL/kg at mechanical index 0.4, and placebo 0.1 mL/kg at mechanical index 1.5). Three subjects were excluded from the analysis population: 2

subjects had technically inadequate data due to flash card problems, and one subject had subcutaneous infiltration at the intravenous (i.v.) site on Day 1.

Table 2: Analysis of Maximum Increase From Baseline In QTcI Interval (ms) Within 1 Hour Postdose, Primary Analysis Population, Final Results for Study BR1-113

Parameter	Placebo MI 0.4 (N=50)	Placebo MI 1.5 (N=50)	SonoVue MI 0.4 (N=50)	SonoVue MI 1.5 (N=50)
Baseline^a				
Mean (SD)	403.0 (24.0)	402.4 (24.1)	401.1 (24.7)	402.1 (23.8)
Median	400.0	397.0	399.5	400.0
Min—Max	358–454	360–460	349–454	363–458
Maximum Postdose Value^b				
Mean (SD)	421.4 (26.8)	420.0 (26.5)	420.0 (26.4)	418.8 (25.7)
Median	419.0	418.0	420.5	415.0
Min—Max	364–487	378–486	365–475	375–480
Maximum Increase From Baseline^c				
LS Mean Change (SE)	18.5 (1.3)	17.7 (1.3)	18.9 (1.3)	16.7 (1.3)
95% CI for LS Mean Change	(15.8, 21.1)	(15.0, 20.3)	(16.3, 21.6)	(14.0, 19.3)
Placebo MI 0.4– SonoVue MI 0.4				
Difference in LS Mean Change (SE)			-0.49 (1.59)	
95% CI for Difference of LS Mean Change			(-3.63, 2.66)	
Placebo MI 1.5– SonoVue MI 1.5				
Difference in LS Mean Change (SE)				1.03 (1.59)
95% CI for Difference of LS Mean Change				(-2.11, 4.18)
^a Baseline is the mean of all technically adequate recorded values from 3 hr predose to immediately predose. ^b Postdose value from +1 min to +1 hr where the maximum increase from baseline occurred. ^c Based on an ANOVA model including treatment and period as fixed effects and subject as random effect. QTc Interval Normal Range: 320 - 440 msec MI = Mechanical Index; QTcI = Individual subject corrected QT interval; SD = Standard deviation; SE = Standard error; LS = Least squares; CI = Confidence interval; Min = Minimum; Max = Maximum				
Table data derived from <i>Clinical Trial Report BR1-113</i> .				

Source: ISS, table TT

ECG assessment in both studies: Cardiac electrophysiology: Continuous 12-lead ECG recordings were sent to a core laboratory for analysis. Interval durations for RR, PR, QRS, and QT intervals were calculated based on the 3-beat average at protocol-specified timepoints using manual digitization with verification of interval measurements by board-certified cardiologists who were blinded to identity of study agent. The correction of QT interval was performed using individual subject correction factors and the corrected QT interval was termed QTcI. Each subject's correction factor was calculated based on approximately 50 initial predose (ie, prior to the first administration of study agent) data points that were processed by the core laboratory. Data from the following timepoints were included in the analysis of continuous 12- lead ECG parameters:

Predose:

- Every 30 minutes from 1 to 3 hours predose;

- Every 15 minutes from 1 hour predose to just before study agent administration.

After the start of each study agent administration:

- Every minute for the first 20 minutes (approximately 2 elimination half-lives of SonoVue);
- At 30, 45 and 60 minutes (>5 elimination half-lives of SonoVue);
- Every 30 minutes from 1 to 2 hours; and
- Every 2 hours from 2 to 12 hours.

The continuous 12-lead ECG data were reviewed by the blinded reader (cardiologist) for identification of subjects with pathological U waves, clinically significant T-wave changes, or postdose arrhythmias

Reviewer's comments: In studies BR1-112 and 113, two prospective controlled studies, continuous 12-lead ECG recordings were obtained from 3 hours prior to each dose of study drug through 24 hours postdose. ECGs were centrally read and interval measurement was performed by manual digitization with verification of interval measurements by blinded, board-certified cardiologists.

In both studies mean QTc duration was similar in the placebo and treated groups, post dose QTcI did not exceed 500 ms. Maximal increases from baseline in study 112 were < 30 ms (upper bound of CI was 20 ms). A similar trend was seen in study 113. One subject had a post-baseline increase > 60 ms in study 112; no subject had an increase > 60m s in study 113.

In study 112 one subject, experienced a transient ventricular extrasystoles (PVCs) 1 minute after administration of SonoVue 0.5 mL/kg; the Investigator considered the relationship to study agent to be unknown. This subject also had PVCs at screening ECG. In study 113, thirteen subjects reported PVCs, this was noted at pre and post-dose with similar incidence in placebo and study drug arms. No AEs of concern as per ICHE14 guidance were reported in these studies.

Thank you for requesting our input into the development of this product under NDA. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cdcrpqt@fda.hhs.gov

Therapeutic dose	<p>SonoVue (sulfur hexafluoride microbubbles) is formulated as a 25 mg sterile, non-pyrogenic lyophilized powder (combination of pharmaceutical grade polyethylene glycol [PEG] 4000, phospholipids [PLs] and palmitic acid). The gas phase in the vial is SF₆. After dispersion in 5 mL of sodium chloride injection, USP (0.9% w/v), 1 mL of the dispersion contains 8 µL SF₆ in the microbubbles, equivalent to 45 µg.</p> <p>The recommended dose of SonoVue for left ventricular opacification and endocardial border delineation is 2 mL administered as an intravenous bolus injection during echocardiography. During a single examination, a second injection of 2 mL may be administered when deemed necessary. Each SonoVue injection should be followed by a flush with 5 ml of sodium chloride injection (0.9% w/v), USP.</p>	
Maximum tolerated dose	No mortality, clinical signs or pathological findings seen in rats at 20 mL/kg. (BIO 1/93)	
Principal adverse events	<p>In the 10 clinical pharmacology studies, the most frequently reported adverse reactions were:</p> <ul style="list-style-type: none"> • headache (6 patients) • injection site pain (5 patients) 	
Maximum dose tested	Single dose	The highest single dose tested was 0.3 mL/kg, approximately 10 times the recommended dose (BR1-010).

	Impaired pulmonary function	Compared with healthy subjects: <table border="1"> <thead> <tr> <th>Subjects</th> <th>Mean Cmax (ng/mL)</th> <th>AUC (ng.min/mL)</th> </tr> </thead> <tbody> <tr> <td>Healthy volunteers^a (Study BR1-010)</td> <td>3.17 (geometric)</td> <td>AUC₀₋₆₀ = 9.75</td> </tr> <tr> <td>Impaired pulmonary function (Study BR1-036)</td> <td>1.45 (arithmetic)</td> <td>AUC_{0-∞} = 5.87</td> </tr> </tbody> </table>	Subjects	Mean Cmax (ng/mL)	AUC (ng.min/mL)	Healthy volunteers ^a (Study BR1-010)	3.17 (geometric)	AUC ₀₋₆₀ = 9.75	Impaired pulmonary function (Study BR1-036)	1.45 (arithmetic)	AUC _{0-∞} = 5.87
Subjects	Mean Cmax (ng/mL)	AUC (ng.min/mL)									
Healthy volunteers ^a (Study BR1-010)	3.17 (geometric)	AUC ₀₋₆₀ = 9.75									
Impaired pulmonary function (Study BR1-036)	1.45 (arithmetic)	AUC _{0-∞} = 5.87									
	Hepatic & Renal Impairment	Because SF6 is eliminated via the lungs, no studies of SF6 pharmacokinetics were performed in patients with renal or hepatic impairment. Negligible amounts of SF6 were recovered in the urine of rabbits injected with 0.3 or 1.0 mL/kg of SonoVue.									
Extrinsic Factors	Drug interactions	No specific interaction studies have been performed in humans. In preclinical studies, SonoVue did not interact with the action of aspirin in vitro, or with the action of antihypertensive drugs (captopril, propranolol, or nifedipine), heparin, isosorbide dinitrate, or digoxin in rats in vivo. (Studies SAF 3/97, BRF100, BRF101, BRF102, BRF104) There was no apparent relationship with respect to occurrence of adverse events in the clinical studies for patients receiving various categories of the most common concomitant medications.									
	Food effects	Not assessed									
Expected High Clinical Exposure Scenario	Preclinical data in rabbit show that pharmacokinetics of SF6 is not saturated at least up to a dose of 1 mL/kg approximately 30 times the recommended dose (BIO 1/93). Therefore, Cmax and AUC are expected to increase linearly with the dose up to a dose of 1 mL/kg.										
a Values that are reported are for the 0.3 mL/kg dose in Study BR1-010.											

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/s/

MONICA L FISZMAN
08/22/2012

KEVIN M KRUDYS
08/22/2012

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling and Packaging Review

Date: August 8, 2012

Reviewer: Kevin Wright, PharmD, Safety Evaluator
Division of Medication Error and Prevention Analysis

Acting Team Leader: Yelena Maslov, PharmD, Acting Team Leader
Division of Medication Error and Prevention Analysis

Drug Name and Strength: (Sulfur Hexafluoride Lipid Microsphere)
Kit for Preparation of Injectable Suspension
1.5 to 5.6 x 10⁸ Microsphere per milliliter

Application Type/Number: NDA 203684

Applicant/sponsor: Bracco Diagnostics, Inc.

OSE RCM #: 2012-439

*** This document contains proprietary and confidential information that should not be released to the public.***

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3	Integrated Summary of Medication error risk assesment.....	2
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1 INTRODUCTION

This review evaluates the proposed container label, insert and carton labeling and as well as product design for Sulfur Hexafluoride Lipid Microsphere for NDA 203684 for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

The Applicant submitted NDA 203684 for Sulfur Hexafluoride Lipid Microsphere to the FDA on December 21, 2011. The labels and labeling for this product was submitted on May 11, 2012.

1.2 PRODUCT INFORMATION

The following product information is provided in the December 21, 2011 NDA submission.

- Active Ingredient: Sulfur Hexafluoride Lipid Microsphere
- Indication of Use: Indicated for use in echocardiography in patients with suboptimal echocardiograms to obtain left ventricular opacification and improve endocardial border delineation.
- Route of Administration: Intravenous
- Dosage Form: Injectable Suspension
- Strength: 1.5 to 5.6 10^8 microspheres per milliliter once reconstituted
- Dose and Frequency: Administer 2 mL during examination. A second dose may be administered if necessary.
- How Supplied: Kit for the preparation of Sulfur Hexafluoride Lipid Microsphere. Kit contains a glass vial with Flipcap closure, Mini-Spike (b) (4) transfer system, and 5 mL prefilled syringe of 0.9% sodium chloride.
- Storage: Store kit at room temperature 25° C (77° F).

2 METHODS AND MATERIALS REVIEWED

We reviewed the Sulfur Hexafluoride Lipid Microsphere vial and syringe labels, carton and package insert labeling submitted by the Applicant.

2.1 LABELS AND LABELING

Using the principals of human factors and Failure Mode and Effects Analysis,¹ along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Vial Labels for Sulfur Hexafluoride Lipid Microsphere submitted on May 11, 2012 (Appendix B)
- Kit Carton Labeling submitted on May 11, 2012 (Appendix C)
- Syringe Label for Sodium Chloride Injection, USP (diluent) submitted on May 11, 2012 (Appendix D)
- Shipper Carton Labeling submitted on May 11, 2012 (Appendix E)
- Insert Labeling submitted on December 21, 2011 (no image)

3 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESMENT

Our analysis of the labels and labeling considered the product design, end user, distribution system and environment of use. We noted several deficiencies in the labels and labeling that may lead to confusion.

- The kit for preparation of Sulfur Hexafluoride Lipid Microsphere utilizes a unique transfer system that differs from the marketed imaging products (e.g. Mini-Spike (b)(4)). (b)(4)

[REDACTED]

- The proprietary name acts as the primary identifier in the product selection process. Considering this aspect, the proprietary name should be easily readable and the most prominent item on the labeling. (b)(4)

[REDACTED]

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

(b) (4)

As a result, proprietary name, established name and dosage form should be relocated to appear at the top of the label in a horizontal manner.

4 CONCLUSIONS

DMEPA concludes that the proposed vial label, syringe, shipper and kit carton labeling, can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product to mitigate any confusion.

Additionally, DMEPA concludes that the Section 2.2 (Drug Handling Directions) for the proposed insert labeling needs extensive revisions to make the instructions for preparation of this product user friendly.

5 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

A. Vial Label

(b) (4)

2. Relocate of the proprietary name, established name, and dosage form to the top of the labeling. The proprietary name should read horizontally across the top of the label. (b) (4)
3. To increase the readability of the proprietary name, the proprietary name should be revised to title case (e.g. Sonovue).
4. Ensure the established name follows the proprietary name and is at least ½ the size of the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).
5. Unbold and decrease the font size of the “Rx Only” statement as this statement competes for prominence with other more important information on the principle display panel such as route of administration.
6. Increase the prominence of the statement, “For intravenous use only after reconstitution” by bolding this statement.
7. The vial should be used only once. Therefore, the statement (b) (4) should be revised to read “Single Use Vial. Discard Unused Portion”.

- B. Kit Carton Labeling
1. See comment A.1 through A.5. and revise carton labeling accordingly
- C. Shipper Carton Labeling
1. See comment A.1 through A.5.
- D. Syringe Label for Sodium Chloride Injection, USP (diluent)
1. Revise the Sodium Chloride Syringe Label to state diluent after Sodium Chloride Injection. The label should read, “Sodium Chloride Injection, USP, 0.9% Sodium Chloride (DILUENT)...” to clarify the syringe does not contain any active ingredient.
- E. Insert Labeling
1. Dosage and Administration, Highlights of Full Prescribing Information
 - i. Revise the reference to sodium chloride throughout the text to read as ‘0.9% Sodium Chloride Injection’.
 - ii. Revise the established name to read “Sulfur Hexafluoride Lipid Microsphere” throughout the insert labeling.
 2. Section 2.2 Drug Handling Directions
 - i. Section 2.2 should be revised to separate the instructions for use from the drug handling directions.

(b) (4)
 3. Section 2, Dosage and Administration, (b) (4)
 - i. To ensure the end user recognizes that the special instructions are needed for the preparation of this product, consider including (b) (4)
 - ii. To allow the end user to become more familiar with the product and to mitigate confusion in the preparation of the final product, a diagram identifying each component of the kit (b) (4)
 - iii. To allow the end user to easily follow the instructions, the illustration should immediately follow the text. For example, “Connect the plunger rod to the prefilled syringe barrel by screwing it clockwise into the syringe (See Figure 1)”.

(b) (4)

(b) (4)

- v. Include a statement instructing the end user to follow administration of Sulfur Hexafluoride Lipid Microsphere with 5 mL flush of 0.9% sodium chloride Injection.

If you have further questions or need clarifications, please contact Sandra Griffith, project manager, at 301-796-2445.

APPENDICES

APPENDIX A. DATABASE DESCRIPTIONS

Adverse Event Reporting System (AERS)

The Adverse Event Reporting System (AERS) is a computerized information database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The FDA uses AERS to monitor adverse events and medication errors that might occur with these marketed products. The structure of AERS complies with the international safety reporting guidance ([ICH E2B](#)) issued by the International Conference on Harmonisation. Adverse events in AERS are coded to terms in the Medical Dictionary for Regulatory Activities terminology (MedDRA).

AERS data do have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive all adverse event reports that occur with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, AERS cannot be used to calculate the incidence of an adverse event in the U.S. population.

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

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/s/

KEVIN WRIGHT
08/08/2012

YELENA L MASLOV
08/08/2012

INTRODUCTION

On December 20, 2012, Bracco Diagnostics, Inc. submitted a New Drug Application (NDA 203-684) for SonoVue (sulfur hexafluoride microbubbles) injection. SonoVue is indicated for use in echocardiography in patients with suboptimal echocardiograms to obtain left ventricular opacification and improve endocardial border delineation.

The Division of Medical Imaging Products consulted the Pediatric and Maternal Health Staff to review the Pregnancy, Nursing Mothers, and Pediatric Use subsections of SonoVue labeling.

BACKGROUND

SonoVue (sulfur hexafluoride microbubbles) injection

SonoVue is an ultrasound contrast agent that provides contrast enhancement of the endocardial borders during echocardiography in patients with suboptimal echocardiograms. Factors that affect suboptimal echocardiograms include obesity and chronic obstructive pulmonary disease. The ultrasound waves that are scattered and reflected at the microbubble-blood interface are visualized in the ultrasound image and result in an increased contrast between the blood and the surrounding tissues. The active component in SonoVue microbubbles, SF₆ is eliminated via the lungs. In clinical pharmacology studies at 11 minutes post-dose, approximately 80-90% of the SF₆ content was eliminated.¹

PREA



(b) (4)

SPONSOR PROPOSED LABELING (SUBMITTED DECEMBER 21, 2011)

8 USE IN SPECIFIC POPULATIONS

8.1 PREGNANCY

Pregnancy Category B.



(b) (4)

¹ See draft labeling, submitted December 20, 2011

8.3 NURSING MOTHERS

(b) (4)

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

DISCUSSION

Pregnancy and Nursing Mothers Labeling

The Proposed Pregnancy and Lactation Labeling Rule published in May 2008. While the Final Rule is in clearance, PMHS-MHT is structuring the Pregnancy and Nursing mothers label information in the spirit of the Proposed Rule while still complying with current regulations. The first paragraph in the pregnancy subsection of labeling summarizes available data from published literature, outcomes of studies conducted in pregnant women (when available), and outcomes of studies conducted in animals, as well as the required regulatory language for the designated pregnancy category. The paragraphs that follow provide more detailed descriptions of the available human and animal data, and when appropriate, clinical information that may affect patient management. For nursing mothers, when animal data are available, only the presence or absence of drug in milk is considered relevant and presented in the label, not the amount. The goal of this restructuring is to make the pregnancy and lactation section of labeling a more effective communication tool for clinicians.

No human pregnancy data are available for SonoVue and no adverse effects were observed in animal reproduction studies. No lactation data are available; however, this product is not a radiopharmaceutical and is rapidly cleared via the pulmonary circulation. No specific precautions are necessary for lactating women receiving SonoVue.

Pediatric Use Labeling

The Pediatric Use subsection should clearly describe what is known and what is unknown about use of a drug in children, including limitations of use. This subsection should also highlight any differences in efficacy or safety in children versus the adult population. For products with pediatric indications, pediatric use information should be placed in the specific sections of labeling as warranted. For products without pediatric indications, pediatric use information should be restricted to the pediatric use subsection of labeling, so as not to infer an indication. Any cross-reference from subsection 8.4 Pediatric Use should be directed to pediatric-specific information.

The proposed standard pediatric use regulatory statement is sufficient for SonoVue labeling.

Pediatric Written Request

A Written Request for pediatric studies under the Best Pharmaceuticals for Children Act (BPCA) could be considered if DMIP is aware of potential pediatric use for SonoVue.

PMHS LABELING RECOMMENDATIONS

On July 12, 2012, PMHS attended a labeling meeting with DMIP and agreed on the following labeling for the pregnancy, nursing mothers, and pediatric use subsections of labeling.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B.



8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

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/s/

JEANINE A BEST
07/23/2012

MELISSA S TASSINARI
07/23/2012

LISA L MATHIS
07/24/2012

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 203-684 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: SonoVue Established/Proper Name: SonoVue (sulfur Hexafluoride Microbubbles) Dosage Form: Injection, suspension Strengths: 8 microliters/mL		
Applicant: Bracco Diagnostics Inc. Agent for Applicant (if applicable): N/A		
Date of Application: December 21, 2011 Date of Receipt: December 21, 2011 Date clock started after UN: N/A		
PDUFA Goal Date: October 21, 2012		Action Goal Date (if different): October 19, 2012
Filing Date: February 19, 2012		Date of Filing Meeting: January 31, 2012
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1		
Proposed indication: For use in echocardiography in patients with suboptimal echocardiograms to obtain left ventricular opacification and improve endocardial border delineation.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): 46958				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	X			Standard Review
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
<i>If yes, explain in comment column.</i>				
<i>If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:</i>				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>		<p>X</p>		<p>This is not a 505(b)(2) application</p>
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>				
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs</i></p>				
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p>				
<p>Application No.</p>	<p>Drug Name</p>	<p>Exclusivity Code</p>	<p>Exclusivity Expiration</p>	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at:</p>		<p>X</p>		

http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm				
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>		X		
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDA/NDA efficacy supplements only</i>) If yes, # years requested: 5 years <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	X			
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDA only</i>)?		X		
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>				
Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission , does it follow the eCTD guidance? ¹ If not , explain (e.g., waiver granted).	X			
Index : Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 (<i>NDA/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including: <input checked="" type="checkbox"/> legible	X			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?			X	
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?				
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
<i>If yes, ensure that the application is also coded with the supporting document category, “Form 3674.”</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature?	X			
<i>Certification is not required for supplements if submitted in the</i>				

<i>original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i>				
<i>Note: Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>				
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>			X	Submitted but not applicable
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>			X	
Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC RPM (PeRC meeting is required)²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	X			
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	X			
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?				

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

<i>If no, request in 74-day letter</i>				
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)?	X			
<i>If no, request in 74-day letter</i>				
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>		X		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	X			
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the DCRMSRMP mailbox</i>			X	
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	X			
Is the PI submitted in PLR format? ⁴	X			

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

⁴ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?				
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? <i>(send WORD version if available)</i>			X	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:TBD</i>	X			
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): <i>If yes, distribute minutes before filing meeting</i>			X	

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 7/14/2011 10/6/11 <i>If yes, distribute minutes before filing meeting</i>	X			
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>			X	

ATTACHMENT

MEMO OF FILING MEETING

DATE: January 31, 2012

BLA/NDA/Supp #: 203-684

PROPRIETARY NAME: SonoVue

ESTABLISHED/PROPER NAME: Sulfur Hexafluoride Microbubbles

DOSAGE FORM/STRENGTH: 8 µL/mL

APPLICANT: Bracco Diagnostics Inc.

PROPOSED INDICATION:

For use in echocardiography in patients with suboptimal echocardiograms to obtain left ventricular opacification and improve endocardial border delineation.

BACKGROUND:

SonoVue belongs to the class of ultrasound contrast media (microbubbles) and is used with ultrasound imaging to enhance the echogenicity of the blood.

The proposed indication is for use in echocardiography in patients with suboptimal echocardiograms to obtain left ventricular opacification and improve endocardial border delineation.

SonoVue was originally submitted as NDA 21315 on January 29, 2001, (b) (4)
Since then, there has been communication between FDA and the applicant, the most recent being the Type C meetings on July 16, and October 6, 2011.

SonoVue is currently approved for intravenous use in 36 countries throughout the world, outside USA, and is marketed in 25 countries, indicated for use with echocardiography to provide opacification of cardiac chambers and enhancement of left ventricular endocardial border delineation. An estimated (b) (4) patients have been exposed to SonoVue from 2001 through 2011.

This submission is provided entirely in eCTD (electronic Common Technical Document) format.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Frank Lutterodt	Y
	CPMS/TL:	Kyong Kang	N
Cross-Discipline Team Leader (CDTL)	Alexander Gorovets		Y
Clinical	Reviewer:	Scheldon Kress	Y
	TL:	Alexander Gorovets	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		N
	TL:		N
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		N
	TL:		N
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		N
	TL:		N
Clinical Pharmacology	Reviewer:	Christy John	Y
	TL:	Gene Williams	Y
Biostatistics	Reviewer:	Satish Misra	Y
	TL:	Jyoti Zalkikar	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Sunday Awe	Y
	TL:	Adebayo Lanionu	N
Statistics (carcinogenicity)	Reviewer:		N
	TL:		N
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:		N
	TL:		N
Product Quality (CMC)	Reviewer:	Milagros Salazar Driver	Y

	TL:	Ali Al Hakim	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	Vinayak Pawar	Y
	TL:	Bryan Riley	N
CMC Labeling Review	Reviewer:		N
	TL:		N
Facility Review/Inspection	Reviewer:	Zhong Li	Y
	TL:		N
OSE/DMEPA (proprietary name)	Reviewer:	Kevin Wright	N
	TL:	Todd Bridges	Y
OSE/DRISK (REMS)	Reviewer:		
	TL:		N
OC/OSI/DSC/PMSB (REMS)	Reviewer:		N
	TL:		N
Bioresearch Monitoring (OSI)	Reviewer:		N
	TL:		N
Controlled Substance Staff (CSS)	Reviewer:		N
	TL:		N
Other reviewers	Rafel Dwaine Rieves (Director, DMIP) Shaw Chen (Deputy Office Director)		Yes Yes
Other attendees	Sandra Griffith, Safety PM, OSE		

FILING MEETING DISCUSSION:

GENERAL	
<ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

If no , explain:	
<ul style="list-style-type: none"> Electronic Submission comments List comments:	<input type="checkbox"/> Not Applicable
CLINICAL	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
Comments:	<input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? If no , explain:	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? Comments: <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> Abuse Liability/Potential Comments:	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? Comments:	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
CLINICAL MICROBIOLOGY	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE

Comments:	<input type="checkbox"/> Review issues for 74-day letter
CLINICAL PHARMACOLOGY	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
Comments:	<input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
BIOSTATISTICS	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
Comments:	<input checked="" type="checkbox"/> Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
Comments:	<input type="checkbox"/> Review issues for 74-day letter
IMMUNOGENICITY (BLAs/BLA efficacy supplements only)	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
Comments:	<input type="checkbox"/> Review issues for 74-day letter
PRODUCT QUALITY (CMC)	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
Comments:	<input type="checkbox"/> Review issues for 74-day letter
<u>Environmental Assessment</u>	<input type="checkbox"/> Not Applicable
<ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
If no , was a complete EA submitted?	<input type="checkbox"/> YES <input type="checkbox"/> NO
If EA submitted , consulted to EA officer (OPS)?	<input type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	
Quality Microbiology (for sterile products)	<input type="checkbox"/> Not Applicable

<ul style="list-style-type: none"> Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> Establishment(s) ready for inspection? Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>CMC Labeling Review</u></p> <p>Comments:</p>	<input type="checkbox"/> Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
<p>Signatory Authority: Charles Ganley</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional):</p> <p>Comments:</p>	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):

	<u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
<input type="checkbox"/>	Other

<u>Frank Lutterodt</u>	<u>February 17, 2012</u>
Regulatory Project Manager	Date

<u>Kyong Kang</u>	<u>February 17, 2012</u>
Chief, Project Management Staff	Date

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

/s/

FRANK A LUTTERODT
02/17/2012

KYONG A KANG
02/23/2012