CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203684Orig1s000

CHEMISTRY REVIEW(S)

MEMORANDUM – ADDENDUM to CMC Review # 3.

Date: 8-Oct-2014
From: Milagros Salazar Driver, Ph.D., ONDQA, Div. III, Branch VII
Through: Eldon Leutzinger, Ph.D., ONDQA, Div. III, Branch VII
Danae Christodoulou, Ph.D., ONDQA, Div III, Branch VII
To: NDA 203- 684 File
Subject: Correction of Lumason strength and revision of labeling accordingly.

Summary

During the first cycle of approval the strength of the vials was assigned as 25 mg powder. During the second review cycle, the resubmission, it was decided by the CMC review team to incorporate the amount present of sulfur hexafluoride (SF_6), mg, in the vial prior to reconstitution.
The reconstituted product also included the amount of SF_6, µg, along with the number of microspheres in the designation of final product strength.

During the labeling discussions, it was decided to include the abbreviation of mcg instead of µg and inadvertently, the mcg was substituted in the vial label and carried into the review.
In addition, the strength of SF_6 in the vial prior reconstitution is revised to consider the target value the specifications ± 2% instead of taking only the top value of the range.

The CMC parts of the labeling in the package insert, vial and carton labels are revised accordingly and attached to the information notes shown below.

The solubility of SF_6 and fraction present in the suspension and microspheres is included as well as the fraction of lipids associated to the microspheres in the description of the product.

Lumason vial - Strength and Container Labels

Data and information for vial strength

Composition of Lumason

Name of ingredients	Per vial	After reconstitution	Function
Sulfur hexafluoride, SF_6 (g)	(b) (4)	8 µL/mL**	Drug substance
Distearoylphosphatidylcholine (DSPC)	0.19 mg	(b) (4)	Drug substance
Dipalmitoylphosphatidylglycerol sodium (DPPG.Na)	0.19 mg		Drug substance
Polyethylene glycol 4000	24.56 mg		(b) (4)
Palmitic acid	0.04 mg		Stabilizer
			(b) (4)

** *Content in the microspheres*

Properties of SF_6

Physical Chemical Characterisation

These data have been extracted from the available literature on sulphur hexafluoride

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General Physical Properties	(all data at 25°C and 1 atmosphere, unless otherwise indicated)	
	Sublimation Point	-63.9°C
	Density (liquid)	1.336 g/cm^3
	Density (gas)	6.07 x 10^{-3} g/cm^3
	Vapour pressure of saturated liquid	2.37 MPa
	Surface tension (at 20°C)	8.02 dyne/cm
	Viscosity (liquid)	0.227 cP
	Viscosity (gas)	0.0158 cP
	Refractive Index	1.00078 n_D
Solubility		
	Sparingly soluble in water	0.0054 v/v at 25°C and 1 atm
	Sparingly soluble in saline	0.0045 v/v at room temperature
	Slightly soluble in alcohol	
Partition Coefficient	log K octanol:water	1.68

Calculations

SF_6 Amount in Lumason vial (containing lipid type-A powder and gas)

SF_6 (g) has a density (mass/volume) of 6.07 x 10^{-3} g/cm^3 (or g/mL) at 25ºC and (b) (4)

The testing specifications for the headspace in vial, before reconstitution, are:
(b) (4) mg/mL shelf -life and
(b) (4) mg/mL release
Corresponding to a target value of 6.07 ± 2% at release.

Therefore, the amount per vial (10 mL volume capacity) is 60.7 mg ± 2%

Note: in original review #3, the high value (b) (4) mg/mL of the specification was selected and (b) (4) mg strength (rounded and multiplied by 10 mL vial volume capacity) was assigned as the vial strength. (corrected for the mcg typographical error).

SF_6 Solubility in Lumason

The experimental studies show the dissolved SF_6 in the reconstituted product (SF_6 in solution + SF_6 in microspheres) is about 12 µL/mL (68 µg/mL) while the amount of SF_6 in microspheres is 8 µL/mL (45 µg/mL). Calculating the gas solubility v/v in Lumason the following is found:

Solubility of SF_6 in Lumason suspension: (b) (4)

(b) (4)

Regarding the Lipids in suspension:

Fifteen to twenty three percent of the total lipids in the suspension are associated with the microspheres.

PACKAGE INSERT REVISIONS

(b) (4)

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/s/

MILAGROS SALAZAR DRIVER
10/08/2014

ELDON E LEUTZINGER
10/08/2014

DANAE D CHRISTODOULOU
10/09/2014

NDA 203-684

Lumason™
(Sulfur Hexafluoride Lipid-Type A Microspheres)
for Injectable Suspension

(b) (4) **sulfur hexafluoride/25 mg lipid-type A per VIAL**

Reconstituted injectable suspension:
45 µg sulfur hexafluoride/mL
(equivalent to 1.5-5.6 x 10^8 microspheres per mL)

Bracco Diagnostics, Inc.
Princeton, NJ 08540

Milagros Salazar, Ph.D.

Office of New Drug Quality Assessment
Division III, Branch VII

For
Division of Medical Imaging Products, DMIP

CMC Assessment Section

CMC Review Data Sheet

1. NDA 203-684

2. REVIEW # 3

3. REVIEW DATE: 16-Sep-2014 PDUFA Goal Date: 11-Oct-2014

4. REVIEWER: Milagros Salazar, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents (CMC Review #1)	Document Date
Original NDA Submission	21-DEC-2011
Amendment (BL)-Proprietary Name	27-JAN-2012
Amendment – GI-1/General Correspondence	26-APR-2012
Amendment (AL + BL)	11-MAY-2012
(CMC Review #2	
Resubmission/ Class 2 (SD-15)	31-MAY-2013
Quality Response (SD-17)	19-AUG-2013
Quality Response (SD-19)	25-SEP-2013

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Resubmission/ Class 2 (SD-21)	11-APR-2014
Labeling/PI Draft (SD-25)	05-Sep-2014

7. NAME & ADDRESS OF APPLICANT:

Name:	Bracco Diagnostics, Inc.
Address:	259 Prospect Plains Road – Bldg. H Monroe Township, NJ 08831
Representative:	Melanie Benson, M.S. Director, US Regulatory Operations
Telephone:	609-514-2254

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name:	Lumason™ (formerly Sonovue)
b) Non-Proprietary Name:	Sulfur Hexafluoride Lipid-Type A Microsphere
c) Code Name/#:	BR-1

d) Chem. Type/Submission Priority:

- Chem. Type: (1) NME
- Submission Priority: (S) Standard

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1), Resubmission, Class 2.

10. PHARMACOL. CATEGORY: Ultrasound contrast media

11. DOSAGE FORM: For Injectable Suspension (lyophilized powder)

12. STRENGTH/POTENCY: per VIAL: [redacted] (b) (4) SF_6 / 25 mg lipid-type A
Reconstituted injectable suspension: 45 µg SF_6/mL (equivalent to 1.5-5.6 x10^8 microspheres/mL)

13. ROUTE OF ADMINISTRATION: Intravenous

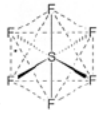
14. Rx/OTC DISPENSED: __√__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed
__√___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

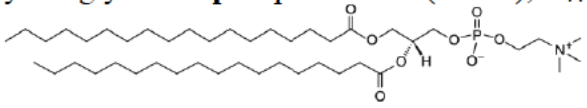
Microsphere Core component (gas)

Sulfur hexafluoride (SF_6) - M.W.: 145.962 g/mol

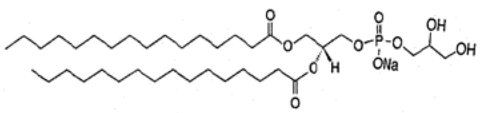


Microsphere Shell Components (lipids)

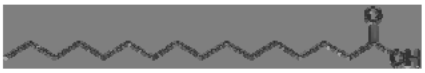
1,2-**Di**stearoyl-*sn*-glycero-3-**p**hospho**c**holine (DSPC), $C_{44}H_{88}NO_8P$ - M.W. 790.6 g/mol



1,2-Dipalmitoyl-*sn*-glycero-3-phospho-*rac*-glycerol sodium (DPPG-Na), $C_{38}H_{74}NaO_{10}P$ - M.W. 745 g/mol



Hexadecanoic acid (Palmitic acid), $C_{16}H_{32}O_2$ - M.W. 256.42 g/mol



B. Other Documents for support or reference:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION – Status
IND	46,958	SonoVue – Active
NDA	21-315	SonoVue – Withdrawn
510(k)	(b) (4)	Mini-Spike® Transfer System

17. STATUS: Update since first review cycle:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Acceptable	10-Oct-2013	Satish Misra, Ph.D.
EES	Overall: PENDING (b) (4) – Acceptable 5/2814 (b) (4) – Acceptable 8/4/14 Vetter – Acceptable 9/12/14 Bracco Suisse – Pending		OC- Robert Wittorf, Pharm.D. Merideth Rose, RPh.
DMEPA*/ OMEPRM***	Proprietary name: Lumason™ Acceptable Product Labels Acceptable with comments	31-Oct-2013 4-Nov-2013 10-Jul-2014	Reasol Agustin, Pharm.D. Carol Holquist, RPh. Neil H Vora Pharm. D. Yelena Maslov, Pharm.D. Lubna A. Merchant, Pharm. D.
OMEPRM/REMS***	Acceptable	2-Sep-2014	Amarilys Vega, M.D., M.P.H.
OPDP**	Acceptable with revision to the PI included.	15-Oct-2013	Emily Baker, Pharm.D.
CDRH consult 510(k)	Acceptable for FDA cleared Mini-Spike (b) (4) – Acceptable (b) (4) functional testing for pre-filled syringe and compatibility - Acceptable	23-Sep-2013 5-Mar-2014	Mary E. Brooks. RN, BSN, MS

* DMEPA: Division of Medication Error Prevention and Analysis

** Office of Prescription Drug Promotion

***Office of Medication Error, Prevention and Risk Management / Risk Evaluation and Mitigation Strategy, REMS

The CMC Review for NDA 203-684

I. Introduction

This Class 2 resubmission of 11-Apr-2014 is in reference to the complete response letter dated 27-Nov-2013 which was based on the deficiencies found during the Bracco Suisse SA, Geneva, Switzerland facility Inspection. The Agency requested to have an update of Module 2 and Modules 3 of the application if resolution of the inspection deficiencies would require new manufacturing and control procedures.

After reviewing this resubmission, Module 2 and Module 3 have been revised to show changes due to correction of inspection deficiencies.

Given the updated information provided and the revision made in Module 2 and 3, this application is recommended for approval pending acceptable overall recommendation from compliance.

II. Summary of CMC Assessment

Lumason™ (sulfur hexafluoride lipid-type A microspheres) for injectable suspension, for intravenous use is an ultrasound contrast agent characterized by a microsphere containing a low solubility gas, sulfur hexafluoride (SF_6) in the core and stabilized by a phospholipid shell.

Lumason is presented as a kit consisting of one Lumason vial for injectable suspension containing 25 mg Lyophilized lipid-type A powder and filled with (b) (4) SF_6 gas, one pre-filled syringe with 5 mL of diluent, 0.9% Sodium Chloride Injection, USP and one Mini-Spike® spike (B. Braun). The reconstituted product has a strength of 45 µg SF_6 per mL equivalent to 1.5-5.6 x10^8 microspheres per mL. The dose recommended is 2 mL in adults.

The NDA has been updated to incorporate additional testing of PEG 4000 by Modulated Differential Scanning Calorimetry (MDSC) for this ingredient. This test determines the (b) (4)

The applicant defined the critical process parameters in their 19-Aug-2013 submission. This NDA resubmission has been updated to reflect incorporation of the changes. For example, (b) (4) has been determined to be a critical quality attribute of the product and these specifications changes have been included in the NDA sections 3.2.P.5.1 and 3.2.P.5.2 as requested. Likewise, the sections 3.2.P. 3.3 and 3.2.P.3.4 have been revised to include the critical process and control parameters.

III. Conclusions/Recommendations

A. Approvability

The application is recommended for Approval based on the revisions provided in Module 2 and Module 3 which reflect the changes in the manufacturing and controls identified by the inspection findings. These changes in specification and process controls reflected in these Modules, have a product conforming with appearance and reconstitution qualities which are acceptable for performance and efficacy for commercial use.

The resolution of the inspectional issues has been finalized and hence, the information update to the NDA based on the acceptance by OC has been reached. For example, the application has been updated according to the stated critical control process parameters to obtain a manufacturing process and product that is under control.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or **Risk Management Steps, if Approvable**

None

IV. Administrative

A. Reviewer's Signature:

(By appended electronic signature page)
Milagros Salazar, Ph.D., CMC Reviewer, ONDQA- Div. III/Branch VII

B. Endorsement Block:

(By appended electronic signature page)
Eldon Leutzinger, Ph.D., CMC Lead, ONDQA- Div. III/Branch VII

(By appended electronic signature page)
Danae Christodoulou, Ph.D., Acting Branch Chief, ONDQA – Div.III/Branch VII

C. CC Block: entered electronically in DARRTS

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/s/

MILAGROS SALAZAR DRIVER
09/16/2014
CMC Recommendation: Approve.

ELDON E LEUTZINGER
09/16/2014

DANAE D CHRISTODOULOU
09/16/2014

INSPECTIONAL ASSIGNMENT
(EMAIL TRANSMITTAL)

Date:	28-Jul-2014
To:	Division of Medical Products and Tobacco Inspections Office of Regulatory Affairs
Facility:	Bracco Suisse SA 31 Route De Le Galaise Plan-Les-ouates, Switzerland FEI No.: 3002740213
Drug Name (dosage form, strength/concentration):	LumaSon (Sulfur Hexafluoride Lipid Microsphere) Injection 1.5-5.6 x 10^8 microspheres/mL reconstituted
Profile Class:	(b) (4)
A/NDA No.:	NDA 203684/000
Chemistry Reviewer	Milagros Salazar Driver, PhD
Microbiology Reviewer (if applicable)	Vinayak B. Pawar, PhD
OC Compliance Officer	Robert Wittorf, PharmD

CDER has identified specific area(s) for inspectional focus for drug product manufacturing in connection with the NDA/203684/000. In accord with the Drug Process Inspections Compliance Program 7356.002 and Pre-Approval Inspection Program Compliance Program 7346.832, PAIs provide for continuity in our pre-market review of drug substance by focusing on areas in which data is questionable; drug characteristics or sensitivities[1] indicate special scrutiny, the overall manufacturing and control strategy appears lacking; and potential manufacturing weaknesses may exist.

Background and Inspectional History

Previous inspection at the Bracco Suisse SA facility was conducted on April 19 to 27, 2012 and was a pre-approval inspection to evaluate the production and control of NDA 203684, Lumason

[1] Examples include heat, moisture, oxygen, or light sensitivity, as well as hygroscopicity, polymorphs, particle size, or other physical characteristics

(Sulfur Hexafluoride Microbubbles). The inspection was classified OAI. During the inspection and subsequent review of the investigation by DIDQ, significant complaints noting a (b) (4) was observed for the product in Chinese and European markets.

Bracco Suisse SA performed an investigation and discovered that (b) (4)

As a result of the firm's investigation, studies concluded that (b) (4)

Due to continued compliance deficiencies, a regulatory meeting was held and a request for additional information was sent to the firm in November 2013. A Complete Response (CR) was subsequently issued for NDA 203684 in November 2013 as the firm had not provided the requested compliance information. Additional compliance information from the firm was provided in December, 2013. In April, 2014 Bracco Suisse SA resubmitted the application for review with a PDUFA date of 11-Oct-2014. Refer to section III for product specific inspectional focus surrounding corrective actions provided by Bracco.

Summary of Product and Manufacturing Process

The finished drug product is indicated for use in echocardiography in patients with suboptimal echocardiograms to obtain left ventricular opacification and improve endocardial border delineation and will be used in a LumaSon (Sulfur Hexafluoride Lipid Microsphere) Injection 1.5-5.6 x 10^8 microspheres/mL reconstituted, lyophilized powder for injection.

Manufacturing Process:

LumaSon (Sulfur Hexafluoride Lipid Microsphere) Injection 1.5-5.6 x 10^8 microspheres/mL reconstituted is an aseptically filled lyophilized powder for injection. The manufacturing process involves multiple steps. Each phase of the manufacturing process is outlined below (sections taken directly from the application).

(b) (4)

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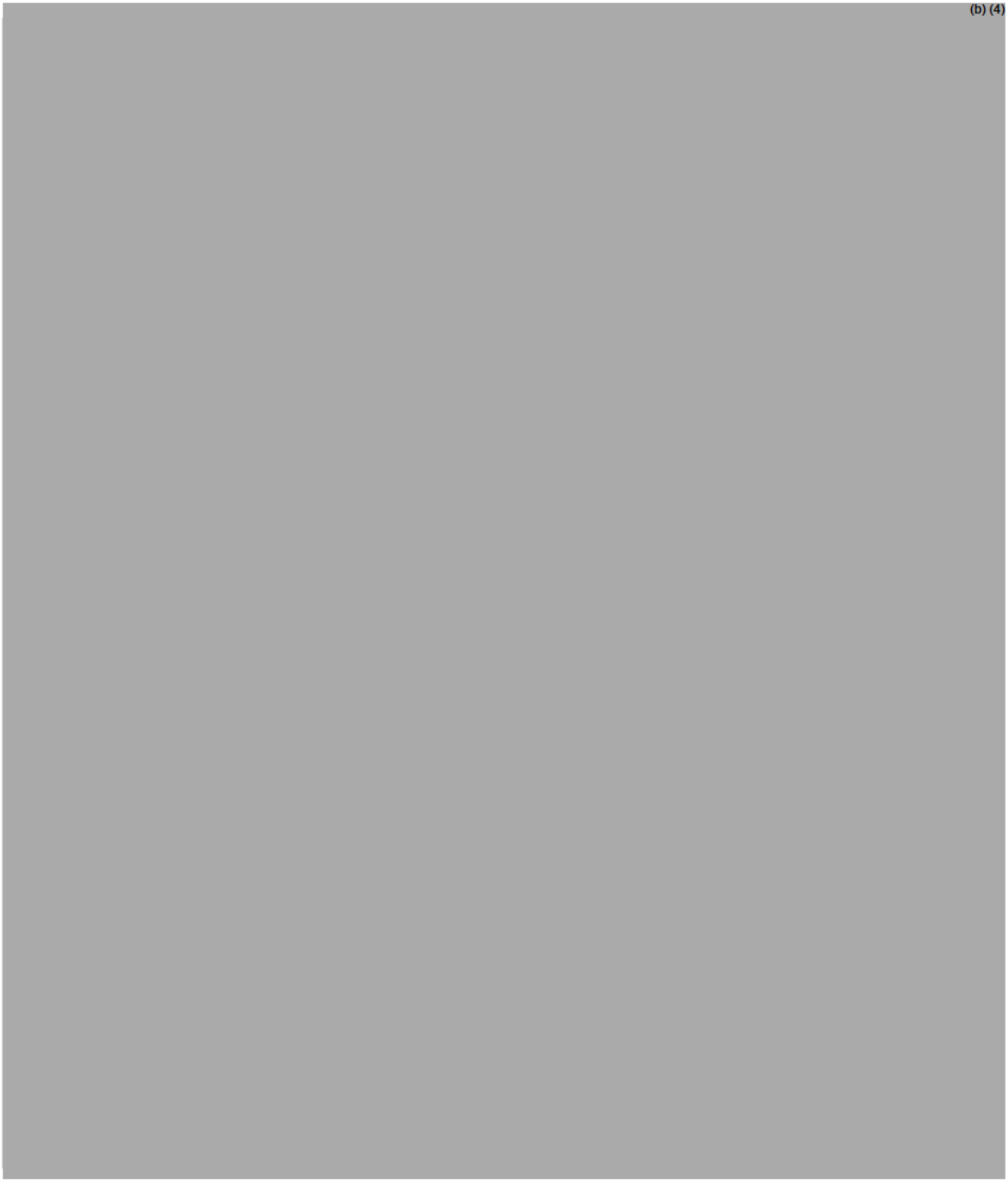
(b) (4)



The following is a brief explanation of product or process specific issues that should receive follow-up during the inspection.

I. Chemistry Review

The Chemistry Reviewer has no information to provide.

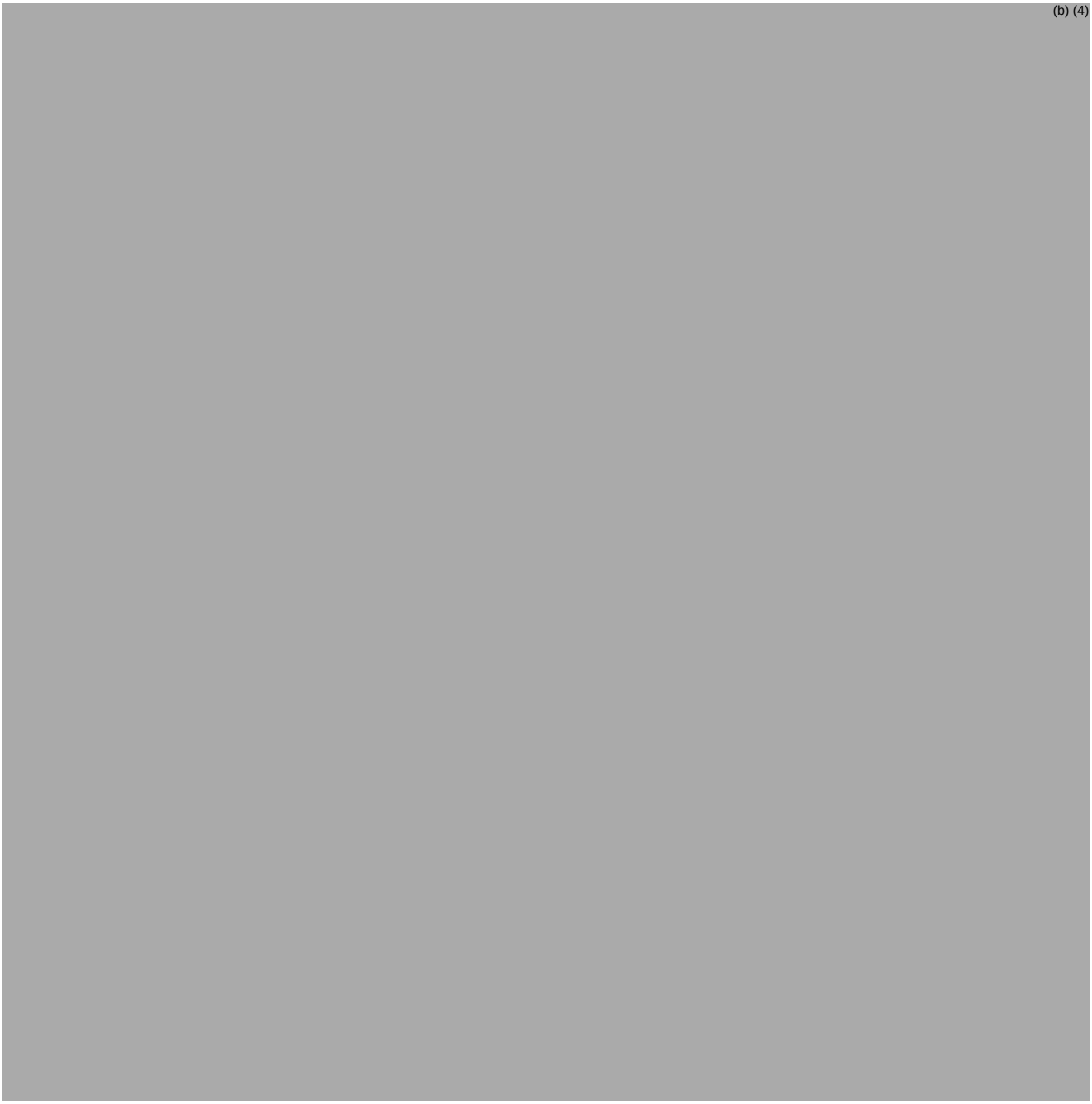
II. Microbiology Review

The microbiology reviewer has no information to provide.

III. Manufacturing and Quality Concerns

During the inspection we encourage the investigator to ensure the firm is adhering to the commitments made by Bracco in the NDA application and inspectional observations based on the 2012 inspection. Bracco Suisse SA provided corrective actions outlined below. Please ensure that the corrective actions are appropriate and ensure that the process meets appropriate quality attributes. Below are specific highlights based on investigational information into (b) (4) provided from Bracco S.A. to CDER, Office of Compliance. Refer also to Attachment I, *Response to FDA letter dated November 10 2013 FEI 3002740213 10Dec13,* for additional details.

(b) (4)



IV. Attachments

Attachment I. *Response to FDA letter dated November 10 2013 FEI 3002740213 10Dec13*

A pre-inspection briefing may be scheduled if additional clarification or background is needed. Should you have questions prior to, during or post inspection, please contact the CDER officials identified above. The CDER Reviewer or Compliance Officer may participate in the inspection. If you would like to request someone from CDER to participate on the inspection, please contact CDER/OC.

Please report your findings regarding these issues in the Establishment Inspection Report (EIR) under the heading, "ADDITIONAL INFORMATION" with the subheading, "Follow-up to CDER PAI Questions."

THIS ASSIGNMENT IS CONFIDENTIAL FDA CORRESONDENCE

cc:
Your Branch Chief, Division Director, and Team Leader (if applicable)
OMPQ Division Director
AD RSI&P
CDER-KTM@fda.hhs.gov
All reviewers listed on first page
Lead investigator (if identified)

If foreign inspection:
DIDQ Division Director and regional DIDQ PAM
DMPTO&I (Ann Marie Montemurro, Susan Laska, Michael Chasey)

OC Doc. No.: KTM-2014-016

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/s/

ROBERT H WITTORF
07/28/2014

MAHESH R RAMANADHAM
08/01/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

MEMORANDUM

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

Date: September 13, 2012

From: LCDR Mary Brooks, RN, BSN, MS
DAGID/GHDB, WO66-G456

Submission: GEN1200158

NDA 203684

Background:
SonoVue is an ultrasound contrast agent characterized by a microbubble structure consisting of a low solubility gas, sulfur hexafluoride (SF6), stabilized by a phospholipid shell. SonoVue is presented as a kit consisting of SonoVue powder for dispersion vial and a SonoVue solvent for dispersion pre-filled syringe. SonoVue powder for injection is a 25 mg sterile, non-pyrogenic lyophilized powder in a (b) (4) sealed vial. A consult request from CDER confirm that the pre-filled syringe meets ISO standards and to review the Mini-spike transfer system which claims to already cleared 510(k) application.

Documents Reviewed:
- 510(k) (b) (4)
- B. Braun's USA website: http://www.bbraunusa.com/products.html?id=00020743040000000375
- B. Braun's Declaration of Conformity(German), dated 2005-05-30
- NDA 203684 Container Closure System 3.2.P.7
- ISO 110404-4 Prefilled Glass Syringes

Review and Discussion:

The NDA's Container Closure System states drug will be packaged as a system with the medication containing vial, drug transfer device (b) (4) glass syringe, a rubber plunger and a (b) (4) closure. The drug transfer device is stated as being a 510(k) cleared device, (b) (4) the Mini-Spike (b) (4) A review of the 510(k) submission did not locate model (b) (4) The submission covers (b) (4) Mini-Spike, (b) (4) (b) (4)

There were no add-to-files submitted by B. Braun for any additional models or changes to the device family. Below is a description of the devices cleared in the submission:

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Recommendations:

- CDRH was not able to locate Mini-Spike [redacted] model in submission [redacted] I would suggest inquiring to the NDA holder to discuss this device issue with B. Braun. CDRH is willing to have a conference call with B. Braun to learn the fundamental differences with the [redacted] model and the other devices cleared under [redacted] and to determine the best regulatory pathway for clearance.
- Follow up with the NDA holder to determine if a [redacted] is incorporated in the Mini-Spike [redacted] transfer device and notify CMC accordingly.
- Determine if the [redacted] closure is an FDA cleared device.
- Request performance compatibility testing for the glass syringe and [redacted]

Reviewer: Mary Brooks

LCDR Mary E. Brooks, RN, BSN, MS
Nurse Consultant

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/s/

FRANK A LUTTERODT

03/07/2014

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

ADDENDUM TO CMC REVIEW #2

NDA 203-684
Lumason (Sulfur Hexafluoride Microsphere) for Injectable Suspension
Bracco Diagnostics, Inc.
CMC section for the CR Letter.
22-Nov-2013

This addendum to CMC Review #2 is filed to update the CMC deficiencies to the complete response letter after the Agency's teleconference with Bracco Diagnostics, Inc. on 20-Nov-2013. The revision for the CMC deficiencies to the CR letter is presented below:

The application has not been updated according to the stated critical control process parameters to show a manufacturing process and product that are under control. The complete revision of Module 2 and Module 3 do not reflect changes in the manufacturing and controls impacted by the inspection findings.

Amend the CMC sections in Module 2 and Module 3 of your application in connection to the current manufacturing and controls as found during the resolution of inspectional deficiencies to support the resolution of past product failures such as, but exclusively, the following:

1. Include the specification for the Appearance test of the Lumason powder product in the vial before reconstitution, referencing the control for [redacted] (b) (4) For example, an acceptance criteria of [redacted] (b) (4) Include this revision in section M3.2.P.5.1 (and corresponding M2 section) of your application.

2. Revise analytical method 405 to include a detailed description of the Appearance test method used to discriminate between [redacted] (b) (4) Include this revision in section M3.2.P.5.2 (and corresponding M2 section) of the application.

3. Update of section M3.2.P.3.3 (and corresponding M2 section) with a flow diagram which includes all in-process controls, especially the ones considered critical as listed in the 19-Aug-2013 submission.

4. Update M3.2.P.3.3-Description of the Manufacturing Process (and corresponding M2 section) to include all temperature and times used during the manufacturing process critical parameters such as those for the [redacted] (b) (4) filling and loading conditions, lyophilization, visual inspection, etc.

5. Update M3.2.P.3.4-Control of the Critical Steps and Intermediates (and corresponding M2 section) to be consistent with the Table of Critical Items in Production Process provided in submission dated 19-Aug-2013.

6. Provide a summary report of changes due to the root cause investigation of product/process failures and how the changes associate with a satisfactory resolution of the quality control of the end product.

7. Provided executed batch record(s) of at least one batch produced with all manufacturing and control changes implemented which demonstrate production of a consistently safe and efficacious product.

8. Provide a copy of the Master Batch Record which has incorporated all the recommended and accepted changes that has both proven to yield a consistent process and product, and is acceptable to the Office of Compliance as part of the resolution of inspectional deficiencies.

9. Provide the control release testing data on the lyophilized vial before reconstitution and after reconstitution products for lot(s) sample(s) manufactured with the implemented changes such as ingredient control (b) (4) The control data should include all testing attributes for both the lyophilized and reconstituted products as described in section 3.2.P.5.1 of your NDA.

10. Provide control release testing data on the lyophilized vial before reconstitution and the after reconstitution products on (b) (4) The control data should include all testing attributes for both lyophilized and reconstituted products as described in section 3.2.P.5.1 of your NDA.

(b) (4)

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/s/

MILAGROS SALAZAR DRIVER
11/21/2013
CMC Recommendation: not approval with a revised list of CMC deficiencies for the CR Letter.

ELDON E LEUTZINGER
11/21/2013

DANAE D CHRISTODOULOU
11/21/2013
I concur with the reviewer's conclusion and recommendations

NDA 203-684

Lumason™
(Sulfur Hexafluoride Lipid Microspheres)
Kit for Preparation of Injectable Suspension

Bracco Diagnostics, Inc.
Princeton, NJ 08540

Milagros Salazar, Ph.D.

Office of New Drug Quality Assessment
Division of Premarketing Assessment III
Branch VII

For
Division of Medical Imaging Products
(DMIP)

CMC Review Data Sheet

1. NDA 203-684

2. REVIEW # 2

3. REVIEW DATE: 6-NOV-2013

4. REVIEWER: Milagros Salazar, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents (CMC Review #1)	Document Date
Original NDA Submission	20-DEC-2011
Amendment (BL)-Proprietary Name-request for review	27-JAN-2012
Amendment – GI-1/General Correspondence	26-APR-2012
Amendment (AL + BL)	11-MAY-2012

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Resubmission/ Class 2 (SD-15)	31-MAY-2013
Quality Response (SD-17)	19-AUG-2013
Quality Response (SD-19)	25-SEP-2013

7. NAME & ADDRESS OF APPLICANT:

Name:	Bracco Diagnostics, Inc.
Address:	107 College Rd. East Princeton, NJ 08540
Representative:	Melanie Benson, M.S. Director, US Regulatory Operations
Telephone:	609-514-2254

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name:	Lumason™
b) Non-Proprietary Name:	Sulfur Hexafluoride Lipid Microsphere
c) Code Name/#:	BR-1

d) Chem. Type/Submission Priority:

- Chem. Type: (1) NME
- Submission Priority: (S) Standard

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1), Resubmission, Class 2.

10. PHARMACOL. CATEGORY: Ultrasound contrast media

11. DOSAGE FORM: Lyophilized Powder for Injectable Suspension, Kit

12. STRENGTH/POTENCY: 8 µL SF_6/mL (equivalent to 45 µg SF_6/mL = (b) (4) (b) (4) microspheres/mL) in reconstituted product. Lyophilized vial: 25 mg.

13. ROUTE OF ADMINISTRATION: Intravenous

14. Rx/OTC DISPENSED: __√__ Rx ___ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed
__√__Not a SPOTS product

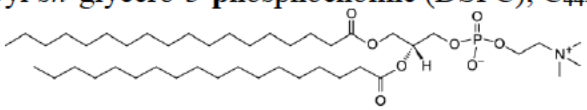
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Microsphere Core component (gas)

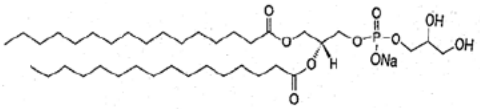
Sulfur hexafluoride (SF_6) - M.W.: 145.962 g/mol

Microsphere Shell Components (lipids)

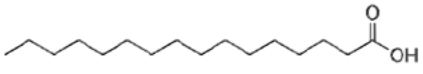
1,2-**D**istearoyl-*sn*-glycero-3-**p**hospho**c**holine (DSPC), $C_{44}H_{88}NO_8P$ - M.W. 790.6 g/mol



1,2-Dipalmitoyl-*sn*-glycero-3-phospho-*rac*-glycerol sodium (DPPG-Na), $C_{38}H_{74}NaO_{10}P$ - M.W. 745 g/mol



Hexadecanoic acid (Palmitic acid), $C_{16}H_{32}O_2$ - M.W. 256.42 g/mol



B. Other Documents for support or reference:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION – Status
IND	46,958	SonoVue – Active
NDA	21-315	SonoVue – Withdrawn
510(k)	(b) (4)	Mini-Spike® Transfer System

17. STATUS: Update since first review cycle:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Acceptable	10-Oct-2013	Satish Misra, Ph.D.
EES	Overall: PENDING (b) (4) – Acceptable 4/2712 (b) (4) – Acceptable 4/27/12 Vetter – Acceptable 10/15/13 Bracco Suisse – Withhold	Pending as of 31-Oct-2013	Merideth Rose
DMEPA*/ OMEPRM***	Proprietary name: Lumason Acceptable	31-Oct-2013	Reasol Agustin, Pharm.D.
OMEPRM/DRISK***	Acceptable	24-Oct-2013	Amarilys Vega, M.D., M.P.H.
OPDP**	Acceptable with revision to the PI included.	15-Oct-2013	Emily Baker, Pharm.D.
CDRH consult 510(k)	Acceptable for FDA cleared Mini-Spike (b) (4)	23-Sep-2013	Mary E. Brooks. Ph.D.

* DMEPA: Division of Medication Error Prevention and Analysis
** Office of Prescription Drug Promotion (formerly DDMAC)
***Office of Medication Error, Prevention and Risk Management / Div. of Risk Management (DRISK)

Chemistry Assessment

The CMC Review for NDA 203-684

I. Introduction

This resubmission of 31-May-2013 is in reference to the complete response letter dated 19-Oct-2012 in which based on the deficiencies found during the Bracco Suisse SA, Geneva, Switzerland facility Inspection, the Agency requested to have an update of Module 2 and Modules 3 of the application if resolution of the inspectional deficiencies would require new manufacturing and control procedures.

After reviewing the resubmission, there was no evidence that Module 2 and Module 3 had been revised to show changes due to correction of inspectional deficiencies. Therefore, the applicant was asked to provide additional CMC information on 25-Jul-2013. See AIR-1 in the Attachment section.

A second CMC information request was transmitted to the applicant during the T-con of 23-Sep-2013 between FDA (DMIP, ONDQA and OC,OMPQ) wherein the 5-Aug-2013 response to OC was discussed. The request was in relation to the need for (b) (4) [redacted] See AIR-2 in the Attachment section.

After CMC #1, the trade name Lumason (formerly SonoVue) has been accepted by DMEPA for sulfur hexafluoride lipid microspheres.

The transfer device changed from the Mini-Spike (b) (4) to the Mini-Spike® both from B.Braun as part of the kit.

This application currently has a withhold recommendation from the District Office and the Office of Compliance.

II. Summary of CMC Assessment

Lumason™ kit for the preparation of sulfur hexafluoride lipid microsphere injectable suspension is an ultrasound contrast agent characterized by a microsphere structure consisting of a low solubility gas, sulfur hexafluoride (SF_6), stabilized by a phospholipid shell.

Lumason is presented as a kit consisting of a Lumason Lyophilized Powder for injection vial, a Lumason diluent, 0.9% Sodium Chloride Injection, pre-filled syringe and a Mini-Spike® spike (B. Braun). Lumason Powder for injectable suspension is a 25 mg sterile, non-pyrogenic lyophilized white powder in a (b) (4) -sealed vial.

The NDA has been updated to incorporate (b) (4) [redacted]

[redacted] (b) (4)

The applicant defined the critical process parameters in their 19-Aug-2013 submission. However, the NDA has not been updated to reflect incorporation of the changes. For example, [redacted] (b) (4) has been determined to be a critical quality attribute but the NDA specifications has not included this test in the NDA sections 3.2.P.5.1 and 3.2.P.5.2. Likewise, the sections 3.2.P. 3.3 and 3.2.P.3.4 have not been revised to include the critical process and control parameters. The applicant needs to provide this information in the NDA. Refer to the CMC portion of the CR letter presented at the end of this review.

In agreement with the OC reviewer, Merideth Rose, the applicant has not revised and captured the critical process and control parameters of the manufacturing process, as described in the 19-Aug-2013 amendment, into the manufacturing batch record (number PF-225, version 09) presented in the NDA. Therefore, the applicant needs to include a revised version of the batch records in the NDA, once the compliance deficiencies are resolved; refer to the CMC portion of the CR letter presented at the end of this review.

The new **spike, Mini-Spike, for the kit is available commercially and functions as a transfer device for reconstitution** of Lumason. The product has a Braun reference # 4550242. (Manufacturer: B. Braun Melsungen AG, Carl-Braun-Strasse 1, 34212 Melsungen, Germany). CDRH consult review for the Mini-Spike found it to be acceptable and supported by the FDA, cleared 510(k) application, [redacted] (b) (4)

III. Conclusions/Recommendations

A. Approvability

The resolution of the inspectional issues has not been finalized and hence, the information update to the NDA based on the acceptance by OC has not been reached. For example, the application has not been updated according to the stated critical control process parameters to obtain a manufacturing process and product that is under control.

The application is not approvable because the District Office and the Office of Compliance have recommended withhold and the complete revision of Module 2 and Module 3 do not reflect changes in the manufacturing and controls impacted by the inspection findings. Refer to the CMC items for the CR, presented at the end of this review.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

IV. Administrative

A. Reviewer's Signature:

(By appended electronic signature page)
Milagros Salazar, Ph.D., CMC Reviewer, ONDQA- Div. III/Branch VII

B. Endorsement Block:

(By appended electronic signature page)
Eldon Leutzinger, Ph.D., CMC Lead, ONDQA- Div. III/Branch VII

(By appended electronic signature page)
Danae Christodoulou, Ph.D., Acting Branch Chief, ONDQA – Div.III/Branch VII

C. CC Block: entered electronically in DARRTS

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

/s/

MILAGROS SALAZAR DRIVER
11/12/2013

ELDON E LEUTZINGER
11/13/2013

DANAE D CHRISTODOULOU
11/13/2013
I concur with the reviewer's conclusion and recommendations

NDA 203-684

SonoVue™
(Sulfur Hexafluoride Lipid Microspheres)
Kit for Preparation of Injectable Suspension

Bracco Diagnostics, Inc.
Princeton, NJ 08540

Milagros Salazar, Ph.D.

Office of New Drug Quality Assessment
Division of Premarketing Assessment III
Branch VII

For
Division of Medical Imaging Products
(DMIP)

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CMC Review Data Sheet

1. NDA 203-684

2. REVIEW # 1

3. REVIEW DATE: 28-AUG-2012

4. REVIEWER: Milagros Salazar, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original IND 46,958 submission active	06-DEC-2007
Original IND 46,958 CMC review	28-AUG-2007
CMC only pre-NDA meeting	06-OCT-2011

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original NDA Submission	20-DEC-2011
Amendment (BL)-Proprietary Name-request for review	27-JAN-2012
Amendment – GI-1/General Correspondence	26-APR-2012
Amendment (AL + BL)	11-MAY-2012

7. NAME & ADDRESS OF APPLICANT:

Name:	Bracco Diagnostics, Inc.
Address:	107 College Rd. East Princeton, NJ 08540
Representative:	Melanie Benson, M.S. Director, US Regulatory Operations
Telephone:	609-514-2254

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: SonoVue™
b) Non-Proprietary Name: Sulfur Hexafluoride Lipid Microsphere
c) Code Name/#: BR-1
d) Chem. Type/Submission Priority:

- Chem. Type: (1) NME
- Submission Priority: (S) Standard

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Ultrasound contrast media

11. DOSAGE FORM: Lyophilized Powder for Injectable Suspension, Kit

12. STRENGTH/POTENCY: 8 µL SF_6/mL (equivalent to 45 µg SF_6/mL = (b) (4) (b) (4) microspheres/mL) in reconstituted product. Lyophilized vial: 25 mg.

13. ROUTE OF ADMINISTRATION: Intravenous

14. Rx/OTC DISPENSED: __√__Rx ___OTC

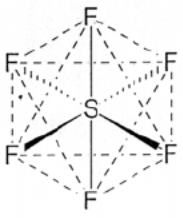
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__√___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

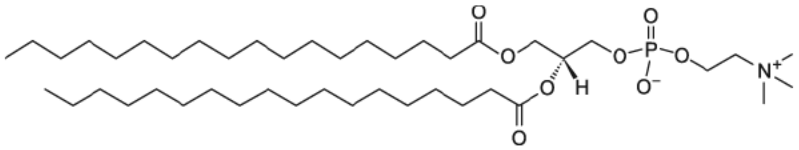
Microsphere Core component (gas)



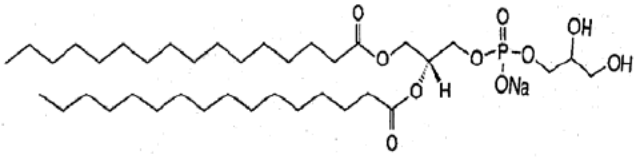
Sulfur hexafluoride (SF_6) - M.W.: 145.962 g/mol

Microsphere Shell Components (lipids)

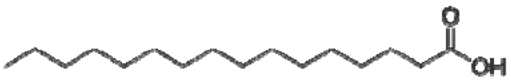
1,2-**Di**stearoyl-*sn*-glycero-3-**p**hospho**c**holine (DSPC), $C_{44}H_{88}NO_8P$ - M.W. 790.6 g/mol



1,2-Dipalmitoyl-*sn*-glycero-3-phospho-*rac*-glycerol sodium (DPPG-Na), $C_{38}H_{74}NaO_{10}P$ - M.W. 745 g/mol



Hexadecanoic acid (Palmitic acid), $C_{16}H_{32}O_2$ - M.W. 256.42 g/mol



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENT
(b) (4)	II		(b) (4)	1	Adequate	11/2003 3/14/2012	LoA 7/16/2009 Review#2 Review# 3
	IV			1	Adequate	11/2003 2/24/2012	LoA 10/5/2011 Review#2 Review #3
	IV			1	Adequate	11/2003 2/16/2012	LoA 10/5/2011 Review#2 Review #3
	III			1,4	Adequate	5/27/2011	LoA 10/18/2010
	III			1,4	Adequate	1/28/2011	LoA 11/16/2010
	III			1,4	Adequate	1/25/2012	LoA 10/6/2010
	III			1,4	Adequate	8/28/2009	LoA 9/1/2010
	III			1.4	Adequate	12/24/2008	LoA 8/11/2011

[1] Action codes for DMF Table:

1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents for support or reference:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION – Status
IND	46,958	SonoVue – Active
NDA	21-315	SonoVue – Withdrawn
510(k)	(b) (4)	Mini-Spike (b) (4) Transfer System

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES (Requested 1/24/12)	PENDING (b) (4) – Acceptable (b) (4) – Acceptable Vetter –VAI Bracco Suisse –OAI	On 8/21/2012	Zhong-Li
Pharm/Tox	Approval		Sunny Awe, Ph.D.
Biopharm	N/A		
LNC	Kit term acceptable based on consultation with Rik Lostritto, Ph.D. and the review team	23-Mar-2012 3-Jul-2012	Milagros Salazar, Ph.D.
Methods Validation	Not recommended according to the current ONDQA policy	13-Mar-2012	Milagros Salazar, Ph.D.
DMEPA* OPDP** Proprietary name	Need revisions to vial , carton & PI. Unacceptable	8-Aug-2012 25-Apr-2012	Kevin Wright, Pharm.D. Carol A. Holquist, R.Ph.
OMEPRM/DRISK***	Acceptable	28-Aug-2012	Amarilys Vega, M.D.
EA	Categorical exclusion (see review)	20-Mar-2012	Milagros Salazar, Ph.D.
Microbiology	Approval	16-Jul-2012	Vinayak B. Pawar, Ph.D.
CDRH consult 510(k)	PENDING-for Mini-Spike		Mary E. Brooks. Ph.D.

* DMEPA: Division of Medication Error Prevention and Analysis
** Office of Prescription Drug Promotion (formerly DDMAC)
***Office of Medication Error, Prevention and Risk Management / Div. of Risk Management

The CMC Review for NDA 203-684

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Based on the chemistry, manufacturing and controls (including microbiological quality), this application is recommended for approval pending satisfactory CDRH device conclusion. However, the facility inspection is still pending and CMC recommendation does not incorporate any potential facility inspection issues.

Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

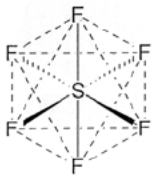
II. Summary of CMC Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

(1) Drug Substance

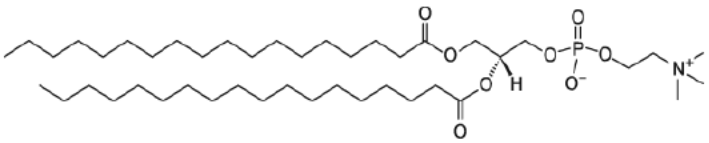
The drug substance is a lipid microspheres formulation consists of three components: a gas component, sulfur hexafluoride (SF_6), and two lipids; 1,2-Distearoyl-*sn*-glycero-3-phosphocholine (DSPC) and 1,2-Dipalmitoyl-*sn*-glycero-3-phospho-*rac*-glycerol sodium (DPPG-Na). Therefore, the microspheres are considered as the drug substance. Palmitic acid as an stabilizer also included in this microsphere formulation.
The drug master files for the above components were reviewed and deemed adequate (see DMFs table above).
The lipid components as well as palmitic acid, a stabilizer, form a single monolayer around the gaseous core. The percentage of DSPC, DPPG.Na and palmitic acid associated to the monolayer is equal to (b) (4) respectively. This microspheres formulation is a powder form and termed SonoVue. After reconstitution of SonoVue powder with normal saline, a suspension of microspheres forms the active moiety to serve as a contrast media for ultrasound imaging techniques. Sulfur hexafluoride, SF_6, is present in the microspheres and also as dissolved gas in the aqueous phase. The total SF_6 content (in solution and in the microspheres) is approximately (b) (4) of SF_6 per mL of SonoVue while the content encapsulated in the microsphere is about 8 µL of SF_6 per mL in the core.

Sulfur hexafluoride with empirical formula SF_6 , has a molecular weight of 145.9 and the following chemical structure:

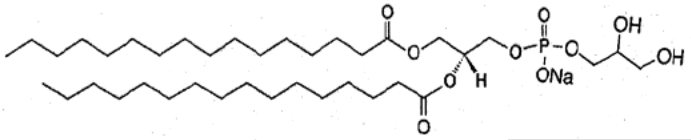


The manufacturer of SF_6 is [redacted] (b) (4) DMF [redacted] (b) (4); authorization letter is provided.

1,2-Distearoyl-*sn*-glycero-3-phosphocholine (DSPC) with empirical formula $C_{44}H_{88}NO_8P$, has a molecular weight of 790.6 and the following chemical structure:



1,2-Dipalmitoyl-*sn*-glycero-3-phospho-*rac*-glycerol sodium (DPPG-Na) with empirical formula $C_{38}H_{74}NaO_{10}P$, has a molecular weight of 745 and the following chemical structure:



The manufacturer of both DSPC and DPPG.Na, is [redacted] (b) (4) – DMF [redacted] (b) (4) and [redacted] (b) (4) respectively; authorization letters are provided.

The sulfur hexafluoride lipid microsphere characteristics are listed below:

Microsphere Characteristics	
Mean diameter range	1.5 – 2.5 µm
Total microspheres concentration	1.5 – 5.6 10^8/mL
Concentration of microspheres between [redacted] (b) (4)	[redacted] (b) (4)
Percent of microspheres ≤ 8 µm	
Percent of microspheres ≤ 10 µm	≥ 99%
Upper size limit	100.0% ≤ 20 µm

(2) Drug Product

SonoVue® (Sulfur Hexafluoride Lipid Microspheres) Kit for the Preparation of Injectable Suspension is an ultrasound contrast agent which contains: (1) 10-mL vial of SonoVue® lyophilized powder, 25 mg, for injectable suspension, (1) 5-mL pre-filled syringe 0.9% Sodium Chloride solvent for reconstitution and (1) Mini-Spike [redacted] (b) (4) as a transfer system. The 3 components of the kit are packaged together in a transparent plastic box.

SonoVue® Lyophilized Powder kit component is formulated as a 25 mg sterile, pyrogen free lyophilized powder in a 10-mL vial. The gas phase in the vial is approximately [redacted] (b) (4)

(b) (4) of SF_6 gas. The lyophilized powder is made of a combination of 24.56 mg polyethylene glycol (PEG) 4000, 0.19 mg of DSPC, 0.19 mg of DPPG.Na and 0.04 mg of palmitic acid.

SonoVue® is filled into (b) (4) glass vials. Each vial is sealed with (b) (4)

SonoVue® Lyophilized Powder is compounded, lyophilized, packaged, labeled and released at the Bracco Suisse site in Geneva, Switzerland.

The manufacturing process involves (b) (4)

Manufacturing and stability data support the quality statements to support a shelf life of 24 months under 25°C/65%RH and 3 hours after reconstitution at CRT.

SonoVue 5-mL pre-filled syringe of 0.9% Sodium Chloride solvent for reconstitution contains 9 mg of sodium chloride per mL.

The manufacturing process is (b) (4) .

SonoVue® solvent pre-filled syringe is manufactured by Vetter Pharma Fertigung GmbH in Revensburg, Germany.

Manufacturing and stability data support the quality statements to support an expiration date of 36 months under 25°C/65%RH.

The Mini Spike (b) (4) is a transfer system used to add the 0.9% sodium chloride into the SonoVue Lyophilized vial for reconstitution and afterwards to withdraw the injectable suspension. The sponsor references a 510(k) application number (b) (4) for this Mini Spike system. CDRH was consulted regarding the status of this device application.

The Mini Spike [redacted] is manufactured by B.Braun AG in Melsungen, Germany.

The microsphere-suspension is prepared before use by injecting through the septum 5 mL of sodium chloride injection, USP (0.9% w/v), to the content of the vial using the transferring device. The vial is then shaken for a few seconds to obtain a white milky, homogeneous suspension. The desired volume of the suspension can be drawn into a syringe any time up to 3 hours after reconstitution. Just before drawing into the syringe, the vial should be agitated to re-suspend the microspheres.

Upon reconstitution, 1 mL of the resulting suspension contains 1.5 to 5.6 x10^8 microspheres/mL, equivalent to 8 µL SF_6/mL (45 µg SF_6/mL), [redacted] DSPC, [redacted] DPPG.Na, [redacted] polyethylene glycol 4000 and [redacted] palmitic acid.

Pertinent physicochemical parameters of SonoVue Injectable Suspension are provided below:

Physicochemical Parameters of SonoVue Injectable Suspension	
Appearance	white milky liquid
pH	4.5 - 7.5
Osmolality (mOsm/kg)	[redacted]
Viscosity (mPa.s)	
Sterility	Sterile
Bacterial endotoxin test	[redacted]

B. Description of How the Drug Product is Intended to be Used

SonoVue (Sulfur Hexafluoride Lipid Microsphere) kit for the Preparation of Injectable Suspension is a diagnostic agent for the enhancement of ultrasound contrast effect in echography. The injectable suspension of SonoVue is administered by intravenous injection.

The recommended dose of SonVue® for left ventricular opacification and endocardial border delineation is 2 mL administered as an intravenous bolus injection during echocardiography followed by a 5 mL flush of sodium chloride injection, USP. A second injection of 2 mL may be administered when necessary. The desired volume of the suspension can be drawn into a syringe any time up to 3 hours after reconstitution. Just before drawing into the syringe, the vial should be agitated to re-suspend the microspheres

C. Basis for Approvability or Not-Approval Recommendation

The application is recommended approval from chemistry, manufacturing and controls point of view under section 505(b)(1) of the Act, based on the information and data

presented in this application supporting the identity, purity, strength and quality of the drug product(s). The applicant has provided adequate information regarding the following CMC requirements:

- Description and controls over the drug substances, excipients and container closures for both the SonoVue lyophilized product and its solvent.
- Characterization and reproducibility of drug substance (microspheres) formation.
- Data on control manufacturing process and reproducibility of lyophilized powder, solvent and reconstituted suspension products.
- Analytical testing and procedures to assure the identity, quality, strength, purity.
- Information on the facilities and methods of production.
- Stability studies in support of 24 months shelf life for SonoVue lyophilized product, 36 months for Sodium chloride pre-filled syringes and 3 hours after reconstitution for SonoVue injectable suspension.
- Product microbiological quality.
- CMC related information in the labeling.

III. Administrative

A. Reviewer's Signature:
(By appended electronic signature page)

Milagros Salazar, Ph.D., Reviewer, ONDQA- Div. III/Branch VII,

B. Endorsement Block:
(By appended electronic signature page)

Eric P. Duffy, Ph.D., Director, ONDQA- Div. III

C. CC Block: entered electronically in DARRTS

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

/s/

MILAGROS SALAZAR DRIVER

09/13/2012

CMC recommendation: Approval, pending satisfactory clearance of the Mini-Spike by CDRH and an overall acceptance by OC of the establishmente inspections for the DS and DP.

ERIC P DUFFY

09/13/2012

Initial Quality Assessment
Branch VII
Pre-Marketing Assessment Division III

OND Division:	Division of Medical Imaging Drug Products
NDA:	203-684
Applicant:	Bracco Diagnostics, Inc.
Letter Date:	21 Dec 2011
Stamp Date:	21 Dec 2011
PDUFA Goal Date:	21 Oct 2012
GRMP Primary Rev Date:	02 Sep 2012
Trade Name:	SonoVue™
Established Name:	Sulfur Hexafluoride (SF_6) Microspheres for Injection
Dosage Form:	Kit - Powder for Injection
Strength:	8 µL SF_6/mL (equivalent to 45 µg SF_6/mL and [redacted] (b) (4) microbubbles/mL) in reconstituted product
Route of Administration:	IV
Indication:	For use in echocadiography in patients with suboptimal echocardiograms to obtain left ventricular opacification and improve endocardial border delineation
Application format	Electronic format as an CTD
ChemClassType/Rev Status	1 (NME) / Standard review classification
Regulatory Filing	505 (b)(1)
Related IND	46,958 / Bracco Diagnostics, Inc.
Assessed by:	Milagros Salazar, Ph.D.

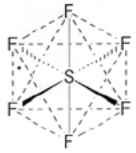
	Yes	No
ONDQA Fileability:	x	
Comments for 74-Day Letter:		x

Background Summary
SonoVue belongs to the class of ultrasound contrast media (ATC class: V08DA) and is used with ultrasound imaging to enhance the echogenicity of the blood. It is a stabilized microbubble preparation for B-mode or Doppler ultrasound. It is intended for use in echocadiography in patients with suboptimal echocardiograms to obtain left ventricular opacification and improve endocardial border delineation. SonoVue is currently approved for intravenous use in 36 countries throughout the world, outside USA, an sis marketed in 25 countries, indicated for use with echocardiography to provide opacification osf cardiac chambers and enhance left ventricular endocardial border delimitation, Doppler of macrovasculature and Doppler of microvasculature. An estimated [redacted] (b) (4) patients have been exposed to SonoVue from 2001 through 2011. The applicant references the meeting minutes of a PreNDA Type C Meeting date 6-Oct-2011.

The microbubble dispersion is prepared before use by injecting through the septum 5 mL of sodium chloride injection, USP (0.9% w/v) to the content of the vial with lyophilized powder containing the active ingredient sulfur hexafluoride gas, lipid and other stabilizing microbubble components. The vial is then shaken for a few seconds to obtain a homogeneous dispersion. The desired volume of the dispersion can be drawn into a syringe any time up to 3 hours after reconstitution. Just before drawing into the syringe, the vial should be agitated to re-suspend the microbubbles. Upon reconstitution as directed, 1 mL of the resulting dispersion contains 8 µL SF6 in the microbubbles, equivalent to 45 µg and 1 to 5 x 10^8 microbubbles/mL with a pH of 4.5 to 7.5.

Drug Substance (DS)

Sulfur hexafluoride, SF_6, is the active ingredient on SonoVue™. Sulfur hexafluoride is a colorless, odorless gas at room temperature and atmospheric pressure. It is slightly soluble in water and saline. Its CAS registration number is 2551-62-4, has a molecular weight of 146.05 and molecular formula is SF_6. Sulfur hexafluoride has an octahedral structure, with Oh point symmetry and a symmetry number of 24. The S-F bond length is 1.564Å and the F-S-F bond angle is 90°.
The molecular structure of SF_6 is the following:



The manufacturer and supplier of SF_6 to be used in SonoVue is:

[redacted] FEI [redacted]; and referenced DMF # [redacted]

SF_6 Stability Lots MP70/02, MP71/02 and MP72/02 are presented in the NDA with data at 25°C for 36 months and at 40°C for 6 months. The retesting period proposed is [redacted]

Drug Substance Critical Issues

- The drug substance DMF ([redacted]) should be reviewed for adequacy. Especially, if the information provided in the NDA is not complete.
- The drug substance impurities should be justified as per ICHQ3A. Any new impurity above the ICH qualification level should be justified by literature reference or by additional pre-clinical studies as appropriate. The CMC reviewer should alert the Pharmacology/Toxicology reviewer regarding any impurities present at levels about those stated in ICH Q3A.

Drug Product (DP)

SonoVue is an ultrasound contrast agent characterized by a microbubble structure consisting of a low solubility gas, sulfur hexafluoride (SF_6), stabilized by a phospholipid shell. SonoVue is presented as a kit consisting of SonoVue powder for dispersion vial and a SonoVue solvent for dispersion pre-filled syringe. SonoVue powder for injection is a 25 mg sterile, non-pyrogenic lyophilized powder in a [redacted] sealed vial. The vial contents include 24.56 mg of Polyethylene glycol 4000 (PEG 4000), 0.19 mg of Distearoylphosphatidylcholine (DSPC), 0.19 mg Dipalmitoyl-phophatidylglycerol sodium (DPPG.Na), 0.04 mg of Palmitic acid and [redacted] of sulfur hexafluoride gas. The solvent in the pre-filled syringe contains 5mL of sterile 0.9% sodium

chloride. The saline pre-filled syringes are used for the reconstitution of SonoVue powder for dispersion for injection for parenteral use.

Each mL of the reconstituted product contains [redacted] PEG 4000, [redacted] DSPC, 0.038 mg DPPG.Na, [redacted] Palmitic acid and 8 µl (equivalent to 45 µg) SF_6. The pH is 4.5 to 7.5. The number of microbubbles per mL is [redacted] the volume of SF_6 if approximately 8 microliters per mL of SonoVue. The mean microbubble diameter is [redacted] with 90 percent of less than [redacted] and 99 percent of less than 11 µm.

SonoVue kit contents: 1 SonoVue lyophilized (SF_6) Microbubbles for Injection, 8 µL/mL

1 Sodium Chloride Injection, USP, 5mL, in pre-filled syringe for SonoVue
1 Mini-Spike [redacted] Transfer System

SonoVue is manufactured for Bracco Diagnostics Inc., Princeton, NJ 08543 by Bracco Suisse SA, (Geneva) Switzerland.

The proposed commercial drug product manufacturing sites are the following:

SonoVue powder vial and secondary packaging of kit:

Bracco Suisse SA
31 Route de la Galaise
1229 Plan-les-Ouates (Geneva)
Switzerland FEI 3002740213

SonoVue solvent pre-filled syringes:
Vetter Pharma Fertigung GmbH & Co. KG
Schuetzenstrasse 87 88212 Ravensburg
Germany FEI 3002270322

The Mini-Spike [redacted] Transfer System is marketed under a 510(k) and is manufactured by:
B.Braun Melsungen AG
Carl-Braun-Strasse 1
34212 Melsungen, Germany Article no.: [redacted] 510(k) no.: [redacted]

Stability data for the Lyophilized Lots: 0A008B, 0A009B and 0A011B, manufactured on April 2000 with data at 25°C/60% RH for 24 months; at 30°C/60% RH for 12 months and at 40°C/75% RH for 6 months are presented in the NDA. The data is provided in support of 24 months shelf life for the lyophilized vial. The stability studies for the SonoVue powder vial also include data on the reconstituted product for up to 6 hours after preparation in support of 3 hours post-reconstitution stated in the labeling.

Stability data for the NaCl 0.9% pre-filled syringes include Lots: 321001, 321002 and 322003 at 25°C/60% RH for 48 months and at 40°C/75% RH for 6 months are presented in the NDA. The data is provided in support of 36 months expiration for the SonoVue solvent.

Drug Product Critical Issues

- Determine if the applicant appropriately established impurity acceptance limits based on ICH Q3B(R2).

- The CMC of the formulation ingredients via their respective DMFs and control specifications from the applicant and manufacturer of the final drug product.
- Assess the stability data of each kit component in terms of individual critical parameters being within specifications.
- The analytical methods and their validation need to be evaluated in detail to assure the methods are adequate for the intended components or function in the formulation.
- The DMFs for drug product container/closure systems need to be reviewed for adequacy.
- The analytical method for the assay and determination of the microspheres numbers and size distribution should be evaluated for the adequate control of these parameters.
- The relevant CMC sections for the proposed labeling should be evaluated.
- Evaluate if the established name and dosage form are appropriately used on the proposed carton and container labels. For example, the term microsphere has been used in the past approval of this type of products.

Fileability Template

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	x		
2	Is the section indexed and paginated adequately?	x		
3	On its face, is the section legible?	x		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	x		
5	Is a statement provided that all facilities are ready for GMP inspection?		x	
6	Has an environmental assessment report or categorical exclusion been provided?	x		Categorical Exclusion for SonoVue™ under 21CFR 25.31(b) is claimed.
7	Does the section contain controls for the drug substance?	x		
8	Does the section contain controls for the drug product?	x		
9	Has stability data and analysis been provided to support the requested expiration date?	x		
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	x		
11	Have draft container labels been provided?	x		
12	Has the draft package insert been provided?	x		

13	Has an investigational formulations section been provided?	x		
14	Is there a Methods Validation package?	x		
15	Is a separate microbiological section included?	x		See microbiology review for filing.

Have all DMF References been identified? Yes (√) No ( )

DMF Number	Holder	Description	LOA Included	Status in DARRTS
(b) (4) Type II	(b) (4)		16-Jul-2009	Active 10-13-2000
(b) (4) Type IV			05-Oct-2011	Active 05/12/2011
(b) (4) Type IV			05-Oct-2011	Active 06/07/1996
(b) (4) Type III			1-Mar-2000	Active 03/06/2000
(b) (4) Type III			16-Nov-2010	Active 10/31/2007
(b) (4) Type III			06-Oct-2010	Active 10/02/1087
(b) (4) Type III			01-Sep-2010	Active 10/31/2007
(b) (4) Type III			11-Aug-2010	Active 04-24-2007

Comments and Recommendations
The application is fileable.
Facilities are entered into EES for inspection. A team review is not recommended for this NDA, because the drug substance and drug product manufacturing processes do not require it.

Comment for 74-days letter:
None

Milagros Salazar, Ph.D. 31-Jan-2012
Senior CMC Reviewer Date

Ali AL Hakim, Ph.D. 31-Jan-2012
Branch Chief Date

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

/s/

MILAGROS SALAZAR DRIVER
02/01/2012
CMC recommendation: NDA is fileable.

ALI H AL HAKIM
02/01/2012