CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203684Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Responsible Organization	Division of Medical Imaging Products (DMIP)
Date	9/28/2014
From	Libero Marzella MD, PhD
Subject	Division Director Summary Review
NDA	203684
Applicant Name	Bracco Diagnostics
Date of Submission	4/11/2014
PDUFA Goal Date	10/11/2014
Proprietary Name **Established (USAN) Name**	Lumason Sulfur hexafluoride lipid-Type A microsphere
Dosage Form **Strength**	For injectable suspension (lyophilized powder) per vial: (b) (4) SF_6 / 25 mg lipid-type A; for reconstituted product: 45 mcg SF_6/mL equivalent to 1.5-5.6x10^8 microspheres/ mL
Indications	For use in patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border.
Regulatory Action	Recommend approval

Material Reviewed/Consulted OND Action Package, including:	**Names of Discipline Reviewers**
Clinical	Scheldon Kress MD
Statistical	Anthony Mucci PhD, Satish Misra PhD
Clinical Pharmacology	Christy John PhD
CMC	Milagros Salazar PhD
Microbiology	Vinayak Pawar PhD
Pharmacology/Toxicology	Sunny Awe PhD
OPDP	Emily Baker PharmD, Zarna Patel PharmD
DMEPA	Yelena Maslov Pharm D, Neil Vora PharmD
DRISK	Amarilys Vega MD
CDRH/GHDB	Mary Brooks RN
PMHS	Ethan Hausman MD

CDRH/GHDB - Center for Devices and Radiological Health/General Hospital Devices Branch
CMC - Chemistry Manufacturing and Controls
DMEPA – Division of Medication Error Prevention and Analysis
DRISK - Division of Risk Management
OND - Office of New Drugs
OPDP - Office of Prescription Drug Promotion
PMHS - Pediatric and Maternal Health Staff

1. Introduction

On April 11, 2014 Bracco Diagnostics resubmitted a 505(b)(1) New Drug Application (NDA) for Lumason (sulfur hexafluoride lipid –Type A microsphere) in response to a November 30, 2013 complete response action taken because of manufacturing deficiencies identified by the agency during the inspection of the Bracco manufacturing facility. This review summarizes my assessment of the approvability of this class 2 resubmission.

Lumason is a new molecular entity classified as an ultrasound contrast agent. Lumason is proposed for use is in patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border.

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

Sulfur hexafluoride lipid-Type A microsphere has been marketed in the European Union since 2001.The applicant submitted an NDA (#21315) on January 29, 2001 (b) (4)

The applicant resubmitted the NDA on July 1 2003 (b) (4)

The applicant did not resubmit the NDA and withdrew it on December 26, 2007.

The applicant submitted the present NDA on December 21, 2011 and resubmitted on May 31, 2013 and April 11, 2014 following complete response actions by the agency

2. Chemistry Manufacturing and Controls

Product Quality

The key issue that this resubmission addresses is incorporation in the NDA of critical process parameters that ensure that the Lumason manufacturing process and product is under control.

I agree with the assessment by the CMC reviewer Dr. Salazar that the applicant has adequately addressed this single most important outstanding issue and I concur with the reviewer's recommendation that the NDA be approved.

The applicant defined the critical process parameters in their August 19, 2013 submission. This resubmission has been updated to reflect incorporation of the new parameters. The appearance of the lyophilized product is a critical quality attribute and changes to the specifications have been included in the NDA along with revised critical process and control parameters. Dr. Salazar notes that the inspectional issues at Bracco's manufacturing facility have also been resolved as determined by the Office of Compliance. The present inspection included validation of methods and verification that product batches met new acceptance criteria.

The previous inspection at the Bracco manufacturing facility in April 2012 was classified as official action indicated (OAI). The applicant had received reports of

(b) (4)

(b) (4)

Regarding Lumason labeling, Dr. Salazar recommended revisions to the non-proprietary name and strength designations, and shelf-life and storage information. The applicant revised the labeling accordingly.

Device components

I concur with the findings of the reviewer from the General Hospital Devices Branch of the Center for Devices and Radiological Health.

Mary Brooks reviewed the present resubmission and determined that the following components of the Lumason kit are acceptable: the 501(k) cleared Mini-Spike (b) (4) transfer device; the (b) (4) the prefilled syringe functional testing and compatibility.

Microbiological Quality

The resubmission contained no new microbiological data and none are needed. In concur with Dr. Pawar's assessment (see review dated July 10, 2012) that from the microbiological sterility perspective the product quality is acceptable. I concur with the reviewer's recommendation to approve the NDA.

For the preparation of the lyophilized powder, (b) (4)

[redacted] The [redacted] drug product diluent (saline) is packaged with the drug product in a ready to use syringe.

3. Nonclinical Pharmacology and Toxicology

I concur with the pharmacology and toxicology reviewer's (Dr. Awe) recommendation to approve the NDA.

The applicant did not include new nonclinical studies and this submission does not require additional nonclinical data. Therefore, the pharmacology/toxicology reviewer Dr. Awe's favorable evaluation of the product's nonclinical safety remains unchanged.

4. Clinical Pharmacology and Biopharmaceutics

I concur with the clinical pharmacology reviewer's (Dr. John) approval recommendation.

There is no new clinical pharmacology information in this NDA and none is needed. Most of the clinical pharmacology information was submitted in the initial NDA 21315 in January 2001. The NDA was found acceptable from the clinical pharmacology perspective. Clinical pharmacology comments were conveyed to the applicant and the applicant adequately addressed all the issues in a resubmission of the NDA in June 2003. A previous NDA 203684 resubmission included data on the effect of sulfur hexafluoride microbubbles on QTc. No concerns were identified.

5. Clinical Microbiology

This section is not applicable to this NDA.

6. Clinical/Statistical Efficacy

I concur with the recommendation by the statistical reviewers Dr. Mucci and Misra and the clinical reviewer Dr. Kress that the NDA be approved.

The present resubmission does not include any new efficacy data or re-analyses of data and none are needed.

7. Safety

I agree with the assessment by the clinical reviewers Dr. Kress and Dr. Ye that the safety update provided by the applicant in this resubmission does not raise any new concerns. Therefore I concur with the reviewers' recommendation to approve the NDA.

Dr. Kress summarizes the post-marketing experience for the estimated (b) (4) patients who have received Lumason from April 1, 2001 through September 30, 2013 as follows: the overall reporting frequency for serious adverse events is 361/(b) (4) and the periodic reporting frequency is similar from the time of the original NDA submission; serious hypersensitivity reactions are reported in 1 out of 10,000 Lumason exposures; and the overall reporting frequency for fatal cases is 18/(b) (4) I agree with the assessment by the clinical reviewer that this safety experience is acceptable for a contrast agent.

8. Advisory Committee Meeting

No advisory committee meeting was needed for this resubmission.

The safety of ultrasound contrast agents as a class was discussed at the 2008 and 2011Cardiovascular and Renal Drugs Advisory Committee meetings. Preclinical data, postmarketing safety studies and data from postmarketing surveillance were extensively discussed at these meetings and led to the conclusion that serious but rare cardiopulmonary reactions occur with Lumason and are similar to reactions that occur with other microbubbles in this pharmacologic class. A boxed warning describes the serious cardiovascular reactions and the anaphylactoid reactions are described in the warnings section of the label. No additional safety studies other than standard surveillance are considered necessary.

9. Pediatrics

The applicant proposes to conduct a study in children 9 to 17 years of age, and requested a partial waiver for children younger than 9 years of age. The FDA Pediatric Research Committee on October 16, 2013 recommended granting the request because the number of children younger than 9 years old with poor noncontrast echocardiography is small and studies are impossible or highly impractical. The Committee also agreed with the Division to grant a deferral for pediatric patients ages 9 to 17 years and agreed to the proposed timelines for the deferred studies.

10. Other Relevant Regulatory Issues

There are no unresolved relevant regulatory issues

Office of Prescription Drug Promotion
The FDA reviewer examined the product labeling primarily from a promotional aspect on October 15, 2013 and the reviewer's recommendations were adopted in the labeling revisions.

Division of Medication Error Prevention and Analysis
The agency approved the proprietary name Lumason on November 4, 2013 subsequent to a complete review by DMEPA.

I concur with the assessment by the DMEPA reviewers that the proposed labels and prescribing information can be improved to clarify information and to increase the readability and prominence of important information. The applicant adopted the agency's recommendations.

Office of Compliance
The successful outcome of the re-inspection of the applicant's manufacturing facility is key for verifying that the Lumason manufacturing process and product is under control. The inspection of the facility included: the process for characterization of PEG 4000 batches; the validation of the method for determining the (b) (4) the review of batch records for adherence to new specifications; and the satisfactory evaluation of other potential factors that might have played a role in the (b) (4) of the lyophilized product.

11. Decision/Risk Benefit Assessment

I agree with the unanimous recommendation of the NDA reviewers that the marketing application for Lumason be approved.

The present NDA resubmission achieved successful resolution of the remaining drug manufacturing deficiencies. The clinical safety update revealed no new issues. The agency recommended revisions to the labels and to the prescribing information and the applicant adopted these changes. The applicant developed the required pediatric study plan and the agency has determined that the plan is satisfactory.

The favorable risk benefit of Lumason for use in patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border has been discussed in reviews of previous submissions.

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/s/

LIBERO L MARZELLA
09/29/2014

Summary Review for Regulatory Action

Date	11/15/2013
From	Libero Marzella MD, PhD
Subject	Division Director Summary Review
NDA # **Supplement #**	203684 15; Class 2 resubmission
Applicant Name	Bracco Diagnostics
Date of Submission	05/21/2013
PDUFA Goal Date	11/30/2013
Proprietary Name / **Established (USAN) Name**	Lumason Sulfur Hexafluoride Lipid Microsphere
Dosage Forms / Strength	Lyophilized powder for injectable suspension, kit. Sterile, nonpyrogenic lyophilized powder (25 mg) in a (b) (4)-sealed vial containing microsphere shell components (lipids) and sulfuhexafluoride gas. Upon reconstitution 1 mL of the suspension contains (b) (4) SF6 in the microsphere core, equivalent to 45 µg SF6 and (b) (4) microspheres/ml
Indications	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.
Action	Complete Response because of unresolved deficiencies at the manufacturing facility.

Material Reviewed **OND Action Package, including**:	**Names of discipline reviewers**
Medical Officer Review	Sheldon Kress, MD
Pharmacology Toxicology Review	Awe Sunny, PhD
Chemistry Manufacturing Controls Review	Milagros Salazar, PhD
Microbiology Review	Vinayak Pawar, PhD
Clinical Pharmacology Review	Christy S John, PhD
Statistical Review	Satish Misra, PhD
CDTL Review	Brenda Ye, MD
Pediatric and Maternal Health	Ethan D Hausman, MD
OSE/DRISK	Amarylis Vega, MD
OSE/DMEPA	Reasol S Augustin, PharmD and Yelena Maslov PharmD
OPDP	Emily Baker, PharmD

OND = Office of New Drugs
OPDP = Office of Prescription Drug Promotion
OSE = Office of Surveillance and Epidemiology
DRISK = Division of Risk Management
CDTL= Cross-Discipline Team Leader

1. Introduction

On May 31 2013, Bracco Diagnostics resubmitted a 505(b)(1) New Drug Application (NDA) for Sulfur Hexafluoride Lipid Microsphere (Lumason). Lumason is an ultrasound contrast agent for use in patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border.

The present NDA resubmission for this new molecular entity is in response to a complete Response Letter issued on October 1, 2012 by FDA following the review of the original (December 20, 2011) NDA. The grounds for the CR action were inspection deficiencies identified by FDA at the Bracco Suisse drug manufacturing facility. The facility had failed to determine the root cause of postmarketing reports received from consumers in the EU relating to (b) (4) and questions about the drug manufacturing lyophilization procedures. A transfer device (Mini-Spike (b) (4)) used to attach a syringe to the drug vial had also been inadequately characterized.

2. Background

Sulfur Hexafluoride Lipid Microsphere has been marketed in the European Union since 2001. The applicant submitted and NDA in 2001 and withdrew it (b) (4)

3. CMC

The resubmission has not adequately addressed critical deficiencies identified in the previous review cycle. As a result the District Office and the Office of Compliance have issued a withhold recommendation. I concur with this recommendation.

The CMC reviewer Dr. Salazar has determined that additional manufacturing and control procedures critical for the quality of the final lyophilized product had been developed to address the inspectional deficiencies identified in the previous review cycle. However, Dr. Salazar concurs with OC that the NDA has not been updated to reflect the incorporation of these changes. As described by the Office of Compliance reviewer, Dr. Rose, the applicant needs to include a revised version of the batch records in the NDA once the compliance deficiencies are resolved.

With regard to transfer device issues, the new Mini-Spike transfer device for reconstitution of Lumason was found to be acceptable by the CDRH consult reviewer and is supported by a cleared 510(k) application.

The assessment of the microbiology reviewer Dr. Pawar remains unchanged from the previous review cycle. Dr. Pawar recommends approval of the NDA from the microbiology product quality perspective.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached in the previous review cycle by the pharmacology/toxicology reviewer Dr. Awe that there are no nonclinical issues for this NDA. No new data were submitted in this resubmission and none were needed

5. Clinical Pharmacology/Biopharmaceutics

I concur with the conclusions reached in the previous review cycle by the clinical pharmacology/biopharmaceutics reviewer Dr. Christy John that there are no clinical pharmacology issues that preclude approval of the NDA. No new data were submitted in this resubmission and none were needed.

6. Clinical Microbiology

This section is not applicable to this application. No clinical microbiology data were included in the submission.

7. Clinical/Statistical-Efficacy

The clinical and statistical reviewers Drs. Kress and Misra pointed out that the submission contained no new efficacy data and none were needed. In the previous review cycle the reviewers reaffirmed the efficacy findings based on three studies that demonstrated the ability of sulfur hexafluoride lipid microspheres to improve the left ventricular endocardial border delineation. Improvement during contrast echocardiography was defined as visualization of at least two additional endocardial border segments compared to non-contrasted echocardiography. In all three studies, complete left ventricular opacification was observed in 52% to 80% of the patients following administration of a 2.0-mL dose.

8. Safety

I concur with the clinical reviewer Dr. Kress that the there has been no evidence of a change in the safety profile of Lumason in the submitted safety update. Dr Kress summarizes data from the clinical trials, cardiac, microvascular and observational studies, post-marketing surveillance and a literature search.

In clinical trials, the overall incidence of adverse reactions was approximately 5%. The most frequently reported adverse events were headache, nausea, and chest pain and discomfort. Most adverse events were mild and resolved spontaneously. There were infrequent hypersensitivity reactions as well as events that could be attributed to the underlying cardiac disease of patients who undergo echocardiography. The serious hypersensitivity and cardio-pulmonary reactions including fatalities reported as postmarketing events have been extensively reviewed for the two ultrasound contrast agents marketed in the US and for Lumason. This safety issue has been discussed at two Advisory Committee meetings. There have been nine such fatality reports for Lumason since its introduction to the market outside

US. These cases are discussed in great detail in the primary clinical review. There have been no new reports over the past several years.

A retrospective study (Study BR1-132) showed Lumason does not seem to increase the risk of serious or fatal events in critically ill patients undergoing echocardiography. Experience from post-marketing surveillance of the estimated (b) (4) patients who have received Lumason shows a total of 335 serious adverse reactions for a reporting rate of (b) (4) Overall I consider this safety profile acceptable.

9. Advisory Committee Meeting

No advisory committee meeting was needed for this submission.

The safety of ultrasound contrast agents as a class was discussed at 2008 and 2011 Cardiovascular and Renal Drugs Advisory Committee meetings. Preclinical data, postmarketing safety studies and data from postmarketing surveillance were extensively discussed at these meetings and led to the conclusion that serious but rare cardiopulmonary reactions occur with sulfur hexafluoride and a are similar to events seen with other microbubbles in this pharmacologic class. A boxed warning describes the serious cardiovascular reactions and the anaphylactoid reactions are described in the warnings section of the label. No additional safety studies other than standard surveillance are considered necessary.

10. Pediatrics

I concur with the assessment by Dr. Awe and Laniyonu that based on a review of the clinical literature neither the excipients nor the reconstituted microbubbles pose any unique pediatric safety concerns other than those cited in the labeling for adults.

I concur with the Pediatric Review Committee (PeRC) that the application triggers the Pediatric Research Equity ACT (PREA) and with the committee's findings that:

- a partial waiver in pediatric patients ages birth to 8 years should be granted because studies in this age group are impossible or highly impractical
- a deferral in pediatric patients ages 9 to 17 years should be granted because the product is nearing to approval in adults
- an indication for left ventricular opacification (in addition to endocardial border delineation) should also be sought.

I concur with the assessment by the Pediatric and Maternal Health Consultant Dr. Hausman that the proposed study of patients ages 9 to 17 is generally acceptable. (b) (4)

11. Other Relevant Regulatory Issues

Risk Management
I concur with the reviewer from the Division of Risk Management Dr. Vega that the present submission does not raise new concerns about the safety profile of sulfur hexafluoride and that the risks posed by the drug can be managed through labeling and routine pharmacovigilance. In its present form the labeling includes a boxed warning for serious cardiopulmonary reactions and a warning for anaphylactoid reactions.

The Office of Prescription Drug Promotion OPDP determined that the proposed proprietary name Lumason is acceptable from a promotional perspective. I concur with the recommendation by the OPDP reviewer (Dr. Baker) to contraindicate the intra-arterial administration of sulfur hexafluoride and to include in the highlights section the information regarding the need for resuscitation equipment and trained personnel to be readily available.

I concur with the assessment by the reviewer (Dr. Reasol) from the Division of Medication Error Prevention and Analysis (DMEPA). Dr Reasol conducted a safety evaluation and determined that there are no concerns with the proposed proprietary name.

12. Labeling

In an 11/12/13 amendment the applicant provided revised prescribing information that is in full agreement with to all the labeling changes recommended by DMIP. I concur with these changes.

I concur with DMEPA's assessment (Dr. Yelena Maslov) that the revised container labels and carton labeling are acceptable from a medication error perspective.

13. Decision/Action/Risk Benefit Assessment

I concur with the recommendation made by the FDA clinical primary and secondary reviewers that the risk benefit of Lumason for the proposed use remains favorable. There are no new toxicology or pharmacology issues.

I concur with the assessment by the Office of New Drug Quality and the Office of Compliance that new manufacturing and control procedures critical for the quality of the final product have not been incorporated in the NDA. For this reason I recommend a CR action for this resubmission.

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/s/

LIBERO L MARZELLA
11/15/2013

Summary Review for Regulatory Action

Date	October 8, 2012
From	Dwaine Rieves, MD
Subject	Division Director Summary Review
NDA/BLA #	NDA: 203-684
Applicant Name	Bracco Diagnostics, Inc.
Date of Submission	December 21, 2011
PDUFA Goal Date	October 21, 2012 (a Sunday; so the action is due on the preceding Friday October 19, 2012)
Proprietary Name / Established (USAN) Name	"Sonovue" was proposed and rejected by FDA Sulfur hexafluoride lipid microspheres
Dosage Forms / Strength	The drug is supplied as a kit that is composed of: a glass vial containing 25 mg powdered sulfur hexafluoride lipid microspheres; a prefilled syringe containing 5 mL saline (diluent); and a transfer device for attaching the syringe to the vial.
Proposed Indication(s)	"SonoVue is indicated for use in echocardiography in patients with suboptimal echocardiograms to obtain left ventricular opacification and improve endocardial border delineation."
Action/Recommended Action	Complete Response

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Scheldon Kress, MD
Statistical Review	Satish Misra, PhD & Jyoti Zalkikar, PhD (TL)
Pharmacology Toxicology Review	Sunny Awe, PhD & Adebaryo Laniyonu, PhD (TL)
CMC Review/OBP Review	Milagros Salazar Driver, PhD
Microbiology Review	Vinayak Pawar,
Clinical Pharmacology Review	Christy John, PhD & Gene Williams, PhD (TL)
DDMAC/DPDP	James Dvorsky
DSI	No inspection
CDTL Review	Alex Gorovets, MD, PhD
OSE/DMEPA	Kevin Wright, PharmD
OSE/DDRE	Not applicable
OSE/DRISK	Amarilys Vega, MD
Pediatric & Maternal Health	Jeanine Best, RN, MSN
Project Management	Frank Luttterodt

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication/DPDP = Division of Professional Drug Promotion
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DRISK=Division of Risk Management/ CDTL=Cross-Discipline Team Leader

Signatory Authority Review Template

1. Introduction

This document summarizes my basis for recommending a Complete Response (CR) issuance to Bracco to complete this original review cycle for "Sonovue." The basis for the CR recommendation is:

1) Manufacturing deficiencies at the manufacturing facility in Switzerland;
2) Insufficient characterization of the transfer device, a component of the kit;
3) Insufficient prescribing information development.

The clinical team found the supplied clinical data were sufficient to support the safety and efficacy of Sonovue and we plan to include recommended prescribing information within a CR letter. This recommended labeling differs in many respects from that proposed by Bracco (simplification of multiple sections and clarification of the Clinical Studies section).

Sonovue is an ultrasound/echocardiography contrast agent that has been marketed in Europe since 2001. The drug consists of a lipid outer shell surrounding a sulfur hexafluoride core (to form a "microsphere") and functions in the same manner as the currently approved echocardiography agents (Definity and Optison). These agents are used in patients with "suboptimal" echocardiograms to facilitate visualization of the left ventricular cavity and delineation of the left ventricular endocardial border (and this application proposed an indication similar to the two currently approved agents). The proposed Sonovue label incorporated the boxed warning and warning section typical for drugs within the class of ultrasound contrast agents.

The proposed drug name, "Sonovue," has been rejected by FDA (b) (4) and the applicant will need to propose a new proprietary name. In this review however, I continue to refer to the drug as Sonovue.

2. Background

Bracco originally submitted an NDA for Sonovue in 2001 and subsequently withdrew the application following the occurrence of serious adverse reactions in the European post-marketing experience. The drug continued to be marketed in Europe however and subsequent post-marketing data have indicated that these serious adverse reactions are very uncommon and the occurrence rate is similar to that for other ultrasound contrast agents. This observation was formed at a 2008 FDA Cardio-Renal Drugs Advisory Committee where Bracco and the manufacturers of approved ultrasound contrast agents summarized their clinical data. This Advisory Committee agreed with FDA that all the ultrasound contrast agents were associated with very uncommon but serious cardiopulmonary reactions that were sometimes fatal; the observation had prompted a boxed warning for the approved agents in 2007.

Based, in part, upon the comments from the 2008 Advisory Committee, Bracco submitted this NDA using the same confirmatory clinical study data (three phase 3 studies) submitted back in 2001 but now with updated safety data and the results of a recently completed study that examined the effects of Sonovue upon pulmonary hemodynamics.

The clinical data in this review package are particularly notable for the extent of post-marketing safety data (from Europe) and the recently completed pulmonary hemodynamics study that showed no important impact of Sonovue on pulmonary hemodynamics. The efficacy of Sonovue was not in dispute back when the drug was reviewed in the 2001 review cycle; still the clinical and statistical team reassessed the three phase 3 studies in a manner more typical for contemporary imaging. Specifically, the team assessed the "added value" of Sonovue to non-contrasted echocardiography in terms of left ventricular endocardial border delineation.

Sonovue is to be supplied as a kit that contains three items:

-a glass vial containing 25 mg powdered Sonovue (microspheres);
-a prefilled syringe containing 5 mL saline (diluent);
-a transfer device ("Mini-Spike (b) (4)") that is used to attach the syringe to the vial.

3. CMC/Device

Dr. Salazar Driver performed the manufacturing review and found most of the manufacturing information sufficient to support Sonovue approval. However, two issues evolved during the cycle that precluded her providing a final approval recommendation:

1) FDA inspection of the Bracco Suisse manufacturing facility found that the company's complaint handling procedures were deficient and the company had yet to resolve complaints relating to "failure to image" and questions about the drug manufacturing lyophilization procedures. The facility had an on-going investigation into these problems and this investigation had not been completed during the review cycle. A 483 was issued and the Office of Compliance issued a Withhold recommendation.

2) The transfer device has been inadequately characterized. Bracco had submitted a statement that indicated the transfer device had previously been cleared by FDA under a B Braun 510k. However, FDA CDRH reviewer Ms. Mary Brooks found that this information was in error and no device characterization information was in the application. For example, FDA was unable to assess whether or not the device contained a (b) (4) (which could impact drug quality). This deficiency needs to be resolved before the application can be approved.

4. Nonclinical Pharmacology/Toxicology

Dr. Sunny Awe noted that FDA had previously reviewed the supplied nonclinical data and found the information sufficient to support the approval. Additionally, nonclinical data were discussed at the 2008 Advisory Committee. The committee discussed the Bracco pig model of

microsphere effects at some length; ultimately the committee concluded that the safety signals from this model were not particularly relevant to humans because of species differences in pulmonary physiology.

The supplied animal toxicology and safety studies, the reproductive toxicology and genotoxicology studies did not provide signals of safety concern. Carcinogenicity studies were not performed (consistent with the practice for most imaging agents). Consequently, the non-clinical team recommended approval.

5. Clinical Pharmacology/Biopharmaceutics

Dr. Christy John reviewed the clinical pharmacology data and found the information supported approval; this was the same observation formed by the clinical pharmacology team in response to the 2001 submission. Dr. John specifically addressed the EKG QT information to the QTc team which noted that QT considerations for echocardiography agents are not particularly relevant since echocardiography must be performed with constant EKG monitoring.

The supplied data supported the sponsor's proposed dose of Sonovue, which includes the option of administering a second dose during a single imaging session.

6. Clinical Microbiology

Dr. Vinayak Pawar reviewed the microbiological aspects of the Sonovue manufacturing process and found these items acceptable; he recommended approval of the application.

7. Clinical/Statistical-Efficacy

I have read the clinical reviews and the statistical review and acknowledge the observed strengths and limitations of the data. Overall, the data support the indication statement and the supportive clinical information we have developed for labeling. We completely revised the proposed clinical studies section of the labeling based upon the major findings from the FDA review. Below is an excerpt from this labeling which succinctly describes the findings; overall, the data robustly demonstrated the added value of Sonovue imaging over non-contrasted imaging among patients with suboptimal echocardiograms.

A total of 191 patients with suspected cardiac disease and suboptimal non-contrast echocardiography received X in three multicenter controlled clinical trials (76 patients in Study A, 62 patients in Study B, and 53 patients in Study C). Among these patients, there were 127 men and 64 women. The mean age was 59 years (range 22 to 96 years). The racial and ethnic representations were 79% Caucasian, 16% Black, 4% Hispanic, <1% Asian, and <1% other racial or ethnic groups. The mean weight was 204 lbs (range 92 to 405 lbs). Approximately 20% of the patients had a chronic pulmonary disorder and 30% had a history of heart failure. Of the 106 patients for whom a New York Heart Association (NYHA)

classification of heart failure was assigned, 49% were Class I, 33% were Class II, and 18% were Class III. Patients with NYHA Class IV heart failure were not included in these studies.

In Studies A and B, each patient received four intravenous bolus injections of X (0.5, 1, 2, and 4 mL), in randomized order. In Study C, each patient received two doses of X (1 mL and 2 mL) in randomized order. All three studies assessed endocardial border delineation and left ventricular opacification. For each patient in each study, echocardiography with X was compared to non-contrast (baseline) echocardiography. A recording of 2D echocardiography was obtained from 30 seconds prior to each injection to at least 15 minutes after dosing or until the disappearance of the contrast effect, whichever was longer. Contrast and non-contrast echocardiographic images for each patient were evaluated by two independent reviewers, who were blinded to clinical information and the X dose. (b) (4) Evaluation of left ventricular endocardial border consisted of segment based assessment involving six endocardial segments and using two apical views (2- and 4-chamber views).

Endocardial Border Delineation and Duration of Useful Contrast Effect

In all three studies, administration of X improved left ventricular endocardial border delineation. The majority of the patients who received a 2.0 mL dose of X had improvement in endocardial border delineation manifested as visualization of at least two additional endocardial border segments. Table 2 demonstrates the improvement in endocardial border delineation following X administration as a reduction in percentage of patients with inadequate border delineation in at least one pair of adjacent segments (combined 2-chamber and 4-chamber view). The results are shown by reader.

Table 2. Reduction in Percentage of Patients with Inadequate Border Delineation

Reader	Study A N = 76		Study B N = 62		Study C N = 53	
	Pre-injection	Post-injection	Pre-injection	Post-injection	Pre-injection	Post-injection
A	60 (79%)	22 (33%)	31 (50%)	12 (19%)	12 (23%)	10 (19%)
B	62 (82%)	29 (37%)	54 (87%)	6 (10%)	45 (85%)	20 (38%)

Following the first appearance of contrast within the left ventricle the mean duration of useful contrast effect ranged from 1.7 to 3.1 minutes.

Left Ventricular Opacification

In all three studies, complete left ventricular opacification was observed in 52% to 80% of the patients following administration of a 2.0-mL dose of X. The studies did not sufficiently assess the effect of X upon measures of left ventricular ejection fraction and wall motion.

8. Safety

The main safety concerns for Sonovue were identified as similar to those for other ultrasound contrast agents: a risk for serious cardiopulmonary reactions and anaphylactoid reactions. In the post-marketing experience (estimated at (b) (4) patients), nine fatal reactions have been reported; Dr. Vega details the overall post-marketing database in her FDA OSE review and finds that the occurrence of serious adverse reactions is not unreasonable for the extent of patient exposure.

The sponsor's main clinical trial safety database consisted of 5,275 patients from 70 completed studies; the most notable finding was the occurrence of a serious hypersensitivity-type reaction in one patient that resolved with therapy. No deaths were related to Sonovue exposure in this clinical trial experience.

In a study that focused upon pulmonary hemodynamics, Sonovue was administered to 36 patients who were undergoing right heart catheterization, including 18 with pulmonary hypertension. Sonovue administration to these patients did not produce important hemodynamic alterations during the pulmonary artery pressure monitoring.

9. Advisory Committee Meeting

This supplement was not presented to an advisory committee. As noted above, the safety aspects were discussed at a 2008 Advisory Committee.

10. Other Relevant Regulatory Issues

Clinical site inspections were not performed in this cycle since the data were reviewed and vetted with respect to any need for inspections in the 2001 review cycle.

(b) (4) the division does not concur with this request and is recommending that the sponsor proposed a pediatric development plan. This request is proposed for inclusion in the CR letter.

No PMR/PMC are anticipated, exclusive of the need for pediatric studies.

11. Decision/Action/Risk Benefit Assessment

I concur with a plan for a Complete Response focused upon the need for resolution of manufacturing facility deficiencies, characterization of the transfer device and the need for revised labeling (the package insert needs revision; the container labels were acceptable).

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

/s/

RAFEL D RIEVES
10/09/2012