# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 203684Orig1s000

# ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

# EXCLUSIVITY SUMMARY

NDA # **203684** SUPPL # HFD #

Trade Name **Lumason**

Generic Name **Sulfur Hexafluoride Lipid-type A microspheres**

Applicant Name **Bracco Diagnostics Inc**.

Approval Date, If Known **October 10, 2014**

**PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

**505(b)(1)**

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

**PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

## PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If

the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently

demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

- **Two prospective Phase II/III studies in 437 patients with known or suspected cardiac disease to determine the efficacy of Lumason over a range of doses (0.5, 1, 2, and 4 mL) in patients with known or suspected cardiac disease referred for 2D transthoracic echocardiography at rest (BR1-011) or during rest and pharmacologically-induced stress (BR1-012). BR1-011tested 4 doses at rest (218 patients) and BR1-012 tested 2 doses at rest and stress (219 patients).**

- **Three confirmatory studies (BR1-019A, BR1-019B, and BR1-013) form the basis for the evaluation of efficacy of Lumason for EBD and LVO. The patients enrolled in these studies are those with suspected cardiac disease and suboptimal border delineation on unenhanced 2D echocardiography at rest and reflect patients receiving ultrasound contrast in current clinical practice and those currently recommended for contrast echocardiography by international professional societies including the American Heart Association (AHA), the American College of Cardiology, and the American Society of Echocardiography (ASE). These studies were performed during 1996-7. These studies included 317 patients of which 191 received Lumason. A total of 866 subjects participated in these studies; 718 received SonoVue and 148 received control only. Among the 718 who received Lumason, 53 received both Lumason and control agent (crossover study BR1-013).**

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug

product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

| | | |
|---|---|---|
| Investigation #1 | YES ☐ | NO ☒ |
| Investigation #2 | YES ☐ | NO ☒ |

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

| | | |
|---|---|---|
| Investigation #1 | YES ☐ | NO ☒ |
| Investigation #2 | YES ☐ | NO ☒ |

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

- **Two prospective Phase II/III studies in 437 patients with known or suspected cardiac disease to determine the efficacy of Lumason over a range of doses (0.5, 1, 2, and 4 mL) in patients with known or suspected cardiac disease referred for 2D transthoracic echocardiography at rest (BR1-011) or during rest and pharmacologically-induced stress (BR1-012). BR1-011tested 4 doses at rest (218 patients) and BR1-012 tested 2 doses at rest and stress (219 patients).**

- **Three confirmatory studies (BR1-019A, BR1-019B, and BR1-013) form the basis for the evaluation of efficacy of Lumason for EBD and LVO. The patients enrolled in these studies are those with suspected cardiac disease and suboptimal border delineation on unenhanced 2D echocardiography at rest and reflect patients receiving ultrasound contrast in current clinical practice and those currently**

**recommended for contrast echocardiography by international professional societies including the American Heart Association (AHA), the American College of Cardiology, and the American Society of Echocardiography (ASE). These studies were performed during 1996-7. These studies included 317 patients of which 191 received Lumason. A total of 866 subjects participated in these studies; 718 received SonoVue and 148 received control only. Among the 718 who received Lumason, 53 received both Lumason and control agent (crossover study BR1-013).**

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

| | | |
|---|---|---|
| Investigation #1 | | ! |
| | | ! |
| **IND # 46958** | YES ☒ | ! NO ☐ |
| | | ! Explain: |

| | | |
|---|---|---|
| Investigation #2 | | ! |
| | | ! |
| IND # **46958** | YES ☒ | ! NO ☐ |
| | | ! Explain: |

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

| | |
|---|---|
| Investigation #1 | ! |
| | ! |
| YES ☐ | ! NO ☐ |

| | |
|---|---|
| Explain: | ! Explain: |
| | |
| Investigation #2 | ! |
| | ! |
| YES ☐ | ! NO ☐ |
| Explain: | ! Explain: |

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: **Frank A. Lutterodt**
Title: **Regulatory Project Manager**
Date: **September 29, 2014**

Name of Office/Division Director signing form: **Libero Marzella, M.D., Ph.D.**
Title: **Division Director**

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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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.**

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/s/

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FRANK A LUTTERODT
09/29/2014

LIBERO L MARZELLA
09/29/2014

### 1.3.3 Debarment Certification

Bracco Diagnostics Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this submission.

M Benson

Melanie Benson
Director US Regulatory Affairs

12/20/11
Date

# ACTION PACKAGE CHECKLIST

## APPLICATION INFORMATION[1]

| | | |
|---|---|---|
| NDA # **203684**<br>BLA # | NDA Supplement #<br>BLA Supplement # | If NDA, Efficacy Supplement Type:<br>*(an action package is not required for SE8 or SE9 supplements)* |
| Proprietary Name: **Lumason**<br>Established/Proper Name: **Sulfur Hexafluoride Lipid-type A microspheres**<br>Dosage Form: **For Injectable Suspension -** (b) (4) | | Applicant: **Bracco Diagnostics Inc**<br>Agent for Applicant (if applicable): |
| RPM: **Frank A Lutterodt** | | Division: **Division of Medical Imaging Products** |

NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

**For ALL 505(b)(2) applications, two months prior to EVERY action:**

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☐ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check:

***Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.***

| | |
|---|---|
| ❖ Actions | |
| • Proposed action<br>• User Fee Goal Date is **October 11, 2014** | ☒ AP ☐ TA ☐ CR |
| • Previous actions *(specify type and date for each action taken)* | ☐ None<br>**Complete Response; 11/27/2013**<br>**Complete Response; 10/19/2012** |
| ❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received?<br>Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____ | ☐ Received |
| ❖ Application Characteristics[3] | |

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.
[2] For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).
[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA .pplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only): **Class 1 NME**
***(confirm chemical classification at time of approval)***

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

| | |
|---|---|
| ❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)* | ☐ Yes ☐ No |
| ❖ Public communications *(approvals only)* | |
| • Office of Executive Programs (OEP) liaison has been notified of action | ☒ Yes ☐ No |
| • Indicate what types (if any) of information were issued | ☐ None<br>☒ FDA Press Release<br>☐ FDA Talk Paper<br>☐ CDER Q&As<br>☒ Other **Information Advisory** |
| ❖ Exclusivity | |
| • Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?<br>• If so, specify the type | ☒ No ☐ Yes |
| ❖ Patent Information (NDAs only) | Yes |
| • Patent Information:<br>Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. | ☒ Verified<br>☐ Not applicable because drug is an old antibiotic. |

## CONTENTS OF ACTION PACKAGE

### Officer/Employee List

| | |
|---|---|
| ❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)* | ☒ Included |
| Documentation of consent/non-consent by officers/employees | ☒ Included |

| | |
|---|---|
| **Action Letters** | |
| ❖ Copies of all action letters *(including approval letter with final labeling)* | Action(s) and date(s)<br>**Approval : 10/10/14**<br>**Complete Response; 11/27/2013**<br>**Complete Response; 10/19/2012** |
| **Labeling** | |
| ❖ Package Insert *(write submission/communication date at upper right of first page of PI)* | |
| • Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)* | ☒ Included |
| • Original applicant-proposed labeling | ☒ Included |
| ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)* | ☐ Medication Guide<br>☐ Patient Package Insert<br>☐ Instructions for Use<br>☐ Device Labeling<br>☐ None |
| • Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)* | ☐ Included |
| • Original applicant-proposed labeling | ☒ Included |
| ❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)* | **Included** |
| • Most-recent draft labeling | ☒ Included |
| ❖ Proprietary Name<br>• Acceptability/non-acceptability letter(s) *(indicate date(s))*<br>• Review(s) *(indicate date(s)* | **11/04/2013, 08/26/2013**<br>**10/31/2013, 08/26/2013,**<br>**4/24/2014** |
| ❖ Labeling reviews *(indicate dates of reviews)*---**PMHS Labeling Review -7/24/2012**<br>❖ **DMIP Medical officer Labeling Reviews:11/04/2013 and 5/31/2014** | RPM: ☒ None<br>DMEPA: ☐ None **08/08/2012, 08/15/2013, 7/10/2014**<br>DMPP/PLT (DRISK): ☒ None<br>OPDP: ☐ None **09/22/2014**<br>SEALD: ☒ None<br>CSS: ☒ None<br>Other: ☐ None **06/11/2014** |
| **Administrative / Regulatory Documents** | |
| ❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)*<br>❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee | **03/02/2012**<br>☐ Not a (b)(2) |
| ❖ NDAs only: Exclusivity Summary *(signed by Division Director)* | ☒ Included |
| ❖ Application Integrity Policy (AIP) Status and Related Documents<br>http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm | |

[4] Filing reviews for scientific disciplines are NOT required to be included in the action package.

| | |
|---|---|
| • Applicant is on the AIP | ☐ Yes ☒ No |
| • This application is on the AIP<br>o If yes, Center Director's Exception for Review memo *(indicate date)*<br>o If yes, OC clearance for approval *(indicate date of clearance communication)* | ☐ Yes ☒ No<br>☐ Not an AP action |
| ❖ Pediatrics *(approvals only)*<br>• Date reviewed by PeRC **October 16, 2013**<br>If PeRC review not necessary, explain: _____ | **Partial Waiver-Birth to 8 years Deferral of studies—9 to 17 years** |
| ❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) *(do not include previous action letters, as these are located elsewhere in package)* | **Yes** |
| ❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes) | |
| ❖ Minutes of Meetings | |
| • If not the first review cycle, any end-of-review meeting *(indicate date of mtg)* | ☒ N/A or no mtg |
| • Pre-NDA/BLA meeting *(indicate date of mtg)* | ☒ No mtg |
| • EOP2 meeting *(indicate date of mtg)* | ☒ No mtg |
| • Mid-cycle Communication *(indicate date of mtg)* | ☒ N/A |
| • Late-cycle Meeting *(indicate date of mtg)* | ☒ N/A |
| • Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)* | |
| ❖ Advisory Committee Meeting(s) | ☒ No AC meeting |
| • Date(s) of Meeting(s) | |
| **Decisional and Summary Memos** | |
| ❖ Office Director Decisional Memo *(indicate date for each review)* | ☐ None **11/22/13 , 10/16/2012** |
| Division Director Summary Review *(indicate date for each review)* | ☐ None **09/29/14, 11/15/2013 and 10/09/12** |
| Cross-Discipline Team Leader Review *(indicate date for each review)* | ☐ None **11/14/2013 and 09/14/2012** |
| PMR/PMC Development Templates *(indicate total number)* | ☒ None |
| **Clinical** | |
| ❖ Clinical Reviews | |
| • Clinical Team Leader Review(s) *(indicate date for each review)* | ☐ No separate review **11/14/2013 and 09/14/2012** |
| • Clinical review(s) *(indicate date for each review)* | **06/11/2014, 11/05/2013, 08/24/2012** |
| • Social scientist review(s) (if OTC drug) *(indicate date for each review)* | ☒ None |
| ❖ Financial Disclosure reviews(s) or location/date if addressed in another review<br>OR<br>If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)* | **See Clinical reviewer's 08/24/2012 review** |
| Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)* | ☒ None |

| | |
|---|---|
| ❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)* | ☒ N/A |
| ❖ Risk Management<br>• REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))*<br>• REMS Memo(s) and letter(s) *(indicate date(s))*<br>• Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)* | ☐ None **09/02/14, 10/24/13 and 08/28/2012** |
| ❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)* | ☐ None requested |
| **Clinical Microbiology** ☒ None | |
| ❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)* | ☐ No separate review |
| Clinical Microbiology Review(s) *(indicate date for each review)* | ☐ None |
| **Biostatistics** ☐ None | |
| ❖ Statistical Division Director Review(s) *(indicate date for each review)* | ☒ No separate review |
| Statistical Team Leader Review(s) *(indicate date for each review)* | ☒ No separate review |
| Statistical Review(s) *(indicate date for each review)* | ☐ None **9/25/14<br>10/10/13<br>09/17/12** |
| **Clinical Pharmacology** ☐ None | |
| ❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)* | ☒ No separate review |
| Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)* | ☒ No separate review |
| Clinical Pharmacology review(s) *(indicate date for each review)* | ☐ None **10/31/2013 and 08/24/2012** |
| ❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)* | ☒ None requested |
| **Nonclinical** ☐ None | |
| ❖ Pharmacology/Toxicology Discipline Reviews | |
| • ADP/T Review(s) *(indicate date for each review)* | ☒ No separate review |
| • Supervisory Review(s) *(indicate date for each review)* | ☒ No separate review |
| • Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)* | ☒ None **08/21/2012, 10/17/2013 and 08/28/14** |
| ❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)* | ☒ None |
| ❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)* | ☒ No carc |
| ❖ ECAC/CAC report/memo of meeting | ☒ None<br>Included in P/T review, page |
| ❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)* | ☒ None requested |

| **Product Quality** ☐ None | |
|---|---|
| ❖ Product Quality Discipline Reviews | |
| • ONDQA/OBP Division Director Review(s) *(indicate date for each review)* | ☒ No separate review |
| • Branch Chief/Team Leader Review(s) *(indicate date for each review)* | ☒ No separate review |
| • Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)* | ☐ None **09/16/14**<br>**11/21/13**<br>**09/13/12** |
| ❖ Microbiology Reviews<br>☒ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)*<br>☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)* | ☐ Not needed<br>**07/16/12** |
| ❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)* | ☐ None **CDRH-09/23/13**<br>**03/05/14** |
| ❖ Environmental Assessment (check one) (original and supplemental applications) | |
| ☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)* | **Reviewed and granted on 9/13/12** |
| ☐ Review & FONSI *(indicate date of review)* | |
| ☐ Review & Environmental Impact Statement *(indicate date of each review)* | |
| ❖ Facilities Review/Inspection | |
| ☒ NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within **2 years** of action date) *(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[5])* | Date completed:<br>☒ Acceptable<br>☐ Withhold recommendation<br>☐ Not applicable |
| ☐ BLAs: TB-EER (date of most recent TB-EER must be within **30 days** of action date) *(original and supplemental BLAs)* | Date completed:<br>☐ Acceptable<br>☐ Withhold recommendation |
| ❖ NDAs: Methods Validation *(check box only, do not include documents)* | ☐ Completed<br>☐ Requested<br>☐ Not yet requested<br>☐ Not needed (per review) |

[5] i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

| Day of Approval Activities | |
|---|---|
| ❖ For all 505(b)(2) applications:<br>• Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) | ☐ No changes<br>☐ New patent/exclusivity *(Notify CDER OND IO)* |
| • Finalize 505(b)(2) assessment | ☐ Done |
| ❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email | ☐ Done |
| ❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter | ☐ Done |
| ❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name | ☐ Done |
| ❖ Ensure Pediatric Record is accurate | ☐ Done |
| ❖ Send approval email within one business day to CDER-APPROVALS | ☐ Done |

| | |
|---|---|
| **From:** | Lutterodt, Frank A |
| **To:** | "Benson Melanie" |
| **Subject:** | RE: Pediatric studies time table |
| **Date:** | Wednesday, October 08, 2014 3:21:00 PM |
| **Attachments:** | Lumason Final PI-labeling 10-8-14.doc<br>Lumason NDA 203684 Carton and Container labeling-msd.pdf |

Dear Ms. Benson,

Please find attached edits to prescribing information and corresponding edits to the Carton and vial labels. Do not hesitate to contact me if you have any questions.

Thank you,

*Frank*

---

Frank Lutterodt, M.S. ¦ Regulatory Health Project Manager ¦ Division of Medical Imaging Products
Office of Drug Evaluation IV ¦ Center for Drug Evaluation and Research ¦ Food and Drug Administration
10903 New Hampshire Avenue, Room 5483 ¦ Silver Spring, MD 20993
Phone: (301) 796.4251 • Fax: (301) 796.9849 ¦ Frank.Lutterodt@fda.hhs.gov

---

**From:** Benson Melanie [mailto:Melanie.Benson@diag.bracco.com]
**Sent:** Friday, October 03, 2014 9:00 AM
**To:** Lutterodt, Frank A
**Subject:** RE: Pediatric studies time table

Dear Mr Lutterodt,

Please find the requested information below.

Best regards, Melanie Benson

---

**From:** Lutterodt, Frank A [mailto:Frank.Lutterodt@fda.hhs.gov]
**Sent:** Thursday, October 02, 2014 3:51 PM
**To:** Benson Melanie
**Subject:** Pediatric studies time table

Melanie, I know we discussed this earlier in the week please plug in the dates for the study time table for Lumason

Final protocol Submission: October 31, 2014
Study completion including blinded read: December 31, 2017
Final report submission: May 31, 2018

Thank you,

*Frank*

Frank Lutterodt, M.S. ¦ Regulatory Health Project Manager ¦ Division of Medical Imaging Products
Office of Drug Evaluation IV ¦ Center for Drug Evaluation and Research ¦ Food and Drug Administration
10903 New Hampshire Avenue, Room 5483 ¦ Silver Spring, MD 20993
Phone: (301) 796.4251 • Fax: (301) 796.9849 ¦ Frank.Lutterodt@fda.hhs.gov



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/s/

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FRANK A LUTTERODT
10/10/2014

## Lutterodt, Frank A

**·om:** Wittorf, Robert
**ɔent:** Wednesday, October 01, 2014 12:29 PM
**To:** Salazar Driver, Milagros; Lutterodt, Frank A
**Cc:** Christodoulou, Danae D; Rose, Merideth
**Subject:** FW: Bracco NDA 203-684

Hi Milagros and Frank,

Currently we are experience difficulties with cutover from EES to the new Inspection Management (IM) System in Panorama. Meredith has reviewed the facility inspection EIR for Bracco and DIDQ will classify it as NAI. Refer to this e-mail chain. Once technical issues have been resolved, Merideth and I will move forward in deeming Bracco acceptable based on inspection and provide an overall recommendation of acceptable for the site and NDA 203684.

However, to ensure business continuity during this cutover, we have been given permission under certain circumstances, to communicate inspectional facility and overall recommendations by e-mail for approaching PDUFA dates. This is one of those circumstances and an interim solution. Please feel free to move on the application with an acceptable recommendation from compliance for facility inspections. The overall recommendation re-evaluation date for the application is 09-Nov-2014.

Please let me know if you have any further questions.

Best,

·\obert Wittorf, PharmD.
Compliance Officer
CDER/OC/OMPQ/DGMPA
10903 New Hampshire Ave
Silver Spring, MD 20993-0002
Office: (240) 402-3113

---

**From:** Rose, Merideth
**Sent:** Wednesday, October 01, 2014 11:32 AM
**To:** Wittorf, Robert
**Cc:** Aldridge, Allison; Mozzachio, Alicia (CDER); CDER International Pre-approval
**Subject:** Bracco NDA 203-684

Hi Robert,
We will be classifying Bracco (b) (4) profile as NAI. Once the system is up and running, I can enter the acceptable recommendation.
Thanks,
Merideth

**From:** Rose, Merideth
**To:** Lutterodt, Frank A
**Cc:** Wittorf, Robert
**Subject:** RE: Lumason (formerly SonoVue)-Sulfur Hexafluoride Microbubbles review Update
**Date:** Monday, August 18, 2014 3:30:50 PM

Hi Frank,

I have no additional information to add regarding an update for the inspection at Bracco. An inspection occurred at the site and no significant issues were noted, this inspection will be scheduled for an expedited review by the DIDQ branch chief and a recommendation will be entered for Bracco by the DIDQ goal date, no later than September 27, 2014. Please let me know if you still need an OMPQ representative to attend this meeting.

Thanks,

Merideth

LCDR Merideth K Rose
FDA/CDER/Office Of Compliance
Office of Manufacturing and Product Quality
Division of International Drug Quality
WO 51, Room 4323
Phone: 301-796-1287

-----Original Appointment-----
**From:** Lutterodt, Frank A
**Sent:** Monday, August 18, 2014 3:17 PM
**To:** Laniyonu, Adebayo A; Marzella, Libero; Williams, Gene M; Zalkikar, Jyoti; Leutzinger, Eldon E; Kress, Scheldon; Misra, Satish; John, Christy; Awe, Sunny; Gorovets, Alex; Krefting, Ira; Wittorf, Robert; Tyson, Rene; Pawar, Vinayak; CDER 160 MTG; Salazar Driver, Milagros; Vega, Amarilys; Rose, Merideth; Christodoulou, Danae D; Fagbami, Modupe; Todd, Nushin F; Lee, Tracey; Ehrlich, Diane T
**Cc:** Maslov, Yelena; LaCivita, Cynthia; Kang, Kyong A; Duffy, Eric P; Ayalasomayajula, Vasantha; Makela, Cristina
**Subject:** Lumason (formerly SonoVue)-Sulfur Hexafluoride Microbubbles review Update
**When:** Tuesday, August 26, 2014 12:00 PM-1:00 PM (UTC-05:00) Eastern Time (US & Canada).
**Where:** CDER WO 1201 conf rm Bldg22 - AR

1. Important Goal Dates

**Primary Review Completion Date: September 16, 2014**

**Date to DD: September 18, 2014**

**Date to OD: September 29, 2014**

**Action Goal Date: October 10, 2014**

| | |
|---|---|
| **From:** | Lutterodt, Frank A |
| **To:** | "Benson Melanie" |
| **Subject:** | RE: Lumason Urgent tcon request |
| **Date:** | Friday, September 26, 2014 11:17:00 AM |
| **Attachments:** | Labeling Questions to FDA (2)msd (3).docx |

Melanie, our comments are embedded here.

Thank you,

*Frank*

---

Frank Lutterodt, M.S. ¦ Regulatory Health Project Manager ¦ Division of Medical Imaging Products
Office of Drug Evaluation IV ¦ Center for Drug Evaluation and Research ¦ Food and Drug Administration
10903 New Hampshire Avenue, Room 5483 ¦ Silver Spring, MD 20993
Phone: (301) 796.4251 • Fax: (301) 796.9849 ¦ Frank.Lutterodt@fda.hhs.gov

---

**From:** Benson Melanie [mailto:Melanie.Benson@diag.bracco.com]
**Sent:** Thursday, September 25, 2014 3:13 PM
**To:** Lutterodt, Frank A
**Subject:** RE: Lumason Urgent tcon request

Thank you!

---

**From:** Lutterodt, Frank A [mailto:Frank.Lutterodt@fda.hhs.gov]
**Sent:** Thursday, September 25, 2014 3:12 PM
**To:** Benson Melanie
**Subject:** RE: Lumason Urgent tcon request

Yes, I did. We plan to provide a written response by tomorrow.

Thank you,

*Frank*

---

Frank Lutterodt, M.S. ¦ Regulatory Health Project Manager ¦ Division of Medical Imaging Products
Office of Drug Evaluation IV ¦ Center for Drug Evaluation and Research ¦ Food and Drug Administration
10903 New Hampshire Avenue, Room 5483 ¦ Silver Spring, MD 20993
Phone: (301) 796.4251 • Fax: (301) 796.9849 ¦ Frank.Lutterodt@fda.hhs.gov

---

**From:** Benson Melanie [mailto:Melanie.Benson@diag.bracco.com]
**Sent:** Thursday, September 25, 2014 2:22 PM
**To:** Lutterodt, Frank A
**Subject:** FW: Lumason Urgent tcon request
**Importance:** High

Hi Frank,

Just checking in to make sure you received this.

---

**From:** Benson Melanie
**Sent:** Thursday, September 25, 2014 8:25 AM
**To:** 'Lutterodt, Frank A'
**Subject:** Lumason Urgent tcon request
**Importance:** High

Dear Mr Lutterodt,

Bracco Diagnostics Inc is in receipt of the Division's Information Request dated September 24, 2014 and have reviewed in detail FDA's comments.
We would like to request an urgent teleconference sometime today to discuss and understand some of FDAs requested changes. Details of our discussion points are included in the attached file.

Please contact the undersigned to arrange a mutually agreeable time between you, Dr Marzella and any other required team members. We look forward to hearing from you and meeting with the team to finalize the verbiage to be included in our labeling.

Best regards,

---



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The information contained in this e-mail and any attachments is confidential and may also be privileged. If you are not the named recipient please notify the sender immediately and delete it from your files. Do not disclose the contents to any other person, use it for any purpose, or store or copy the information in any medium.

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/s/

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FRANK A LUTTERODT
10/10/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203-684

**INFORMATION REQUEST**

Bracco Diagnostics Inc.
Attention: Melanie Benson
Director, U.S. Regulatory Operations
259 Prospect Plains RD.
Monroe Township, NJ 08831

Dear Ms. Benson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for LUMASON (sulfur hexafluoride lipid-type A microspheres) for injectable suspension.

We also refer to your April 11, 2014 resubmission, and to your September 5, 2014 correspondence containing your response to FDA's August 18, 2014 information request. This submission also contains your revised Prescribing Information (PI) and container labels. We have reviewed the submission and have comments and request for changes to your container labels and PI.

1. *Carton label Revisions*: Revise the non-proprietary name & strength designations as follows:

   - Lumason (sulfur hexafluoride lipid-type A microspheres) for injectable suspension, (b) (4) sulfur hexafluoride /25 mg lipid-type A per vial

   Kit contents:
   - 1 vial of Lumason lyophilized powder for injectable suspension, (b) (4) sulfur hexafluoride /25 mg lipid-type A
   - 1 prefilled syringe with Diluent containing 5 mL of Sodium Chloride 0.9% Injection, USP for use during reconstitution
     1 Mini-Spike
   - For intravenous use only after reconstitution. See package….
     Kit components intended for single use.
   - Each vial contains lyophilized powder of lipid-type A blend consisting of 0.19 mg distereoylphosphatidylcholine , 0.19 mg dipalmitoylphosphatidylglycerol sodium, 24.56

mg polyethylene glycol 4000 and 0.04 mg palmitic acid. The headspace of the vial contains (b) (4) sulfur hexafluoride.

- Each ml of Diluent in prefilled syringe contains 9 mg of sodium chloride.
  Store kit components at 25ºC (77ºF)
  Rx …

2. *Vial label revisions*: Revise non-proprietary name & strength designations as shown above for the vial.

- Lumason (sulfur hexafluoride lipid-type A microspheres) lyophilized powder for injectable suspension, (b) (4) sulfur hexafluoride /25 mg lipid-type A per vial
  For intravenous use after reconstitution with 5 mL Diluent, Sodium Chloride 0.9% injection, USP

  Single Use Vial
  After vial reconstitution with 5 mL of diluent, each mL of Lumason contains 1.5-5.6 x $10^8$ microspheres [equivalent to 45 mcg sulfur hexafluoride, 0.038 mg distereoylphosphatidylcholine , 0.038 mg dipalmitoylphosphatidylglycerol sodium, 4.1 mg polyethylene glycol 4000 and 0.008 mg palmitic acid]. The pH of the reconstituted product is 4.5 to 7.5.

  Date & time of reconstitution
  _____
  Discard Unused Portion after 3 hours
  Store at 25ºC (77ºF)

3. *Diluent Initial (peel off) label revisions*: include DILUENT in a prominent manner. For example,

- **DILUENT**
  for suspension of
  Lumason™

  Sodium Chloride
  0.9% Injection, USP,

4. *Final label after dilution revisions*: strength, shelf life and storage information needs to be updated. For example,

- Lumason™
  (sulfur hexafluoride
  lipid-type A microspheres)
  injectable suspension
  for intravenous use
  45 mcg sulfur hexafluoride/mL

(equivalent to 1.5-5.6 x $10^8$ microspheres/mL)

Date & time of reconstitution

_____

Discard Unused Portion after 3 hours
Store at 25ºC (77ºF)

- We recommend adjusting the current numerical markings on the diluent label (i.e., 1 mL, 2 mL, 3 mL, 4 mL, and 5 mL) to align immediately next to the bolded markings on the syringe.

(b) (4)

5. Review the comments in the revised PI (attached) and provide a response by Monday, September 29, 2014.

If you have any questions, please contact me at (301) 796-4251.

Sincerely,

*{See appended electronic signature page}*

Frank Lutterodt, M.S.
Regulatory Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure: Prescribing Information

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FRANK A LUTTERODT
09/24/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203-684

**INFORMATION REQUEST**

Bracco Diagnostics Inc.
Attention: Melanie Benson
Director, U.S. Regulatory Operations
259 Prospect Plains RD.
Monroe Township, NJ 08831

Dear Ms. Benson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lumason (Sulfur Hexafluoride Microbubbles).

We also refer to your April 11, 2014 resubmission, containing the proposed container label, carton labeling and prescribing information as well as product design for the Lumason kit. We have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

A. Kit for Preparation of Lumason Labeling for 5 kits

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

   For example,

5 single use Lumason Kits with each kit containing:

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

   1 Sodium Chloride Injection, USP for use with Lumason

   1 Mini-Spike

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

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

B. Kit for Preparation of Lumason Labeling for 1 kit

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

C. Vial Label

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

   "with Sodium Chloride 0.9% Injection, USP."

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

D. Diluent Label

1. Step 7 in Section 2.2, of Dosage and Administration section of the PI states to withdraw a needed amount of the reconstituted product containing Lumason into a syringe that previously contained Sodium Chloride. As a result, this syringe would hold the actual active ingredient, sulfur hexafluoride after reconstitution. However, the label would continue stating "Sodium Chloride Injection, USP, 0.9% Sodium Chloride (DILUENT)."; thus misbranding the product per 21 U.S.C. 352(i).

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

E. Tall Man Lettering

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

If you have any questions, please contact Frank Lutterodt, Regulatory Project Manager, at (301) 796-4251.

Sincerely,

*{See appended electronic signature page}*

Libero Marzella, M.D., Ph.D.
Director
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

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LIBERO L MARZELLA
08/18/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203-684

**ACKNOWLEDGE –**
**CLASS 2 RESUBMISSION**

Bracco Diagnostics Inc.
Attention: Melanie Benson
Director, U.S. Regulatory Operations
259 Prospect Plains RD.
Monroe Township, NJ 08831

Dear Ms. Benson:

We acknowledge receipt on April 11, 2014, of your April 11, 2014, resubmission to your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lumason (Sulfur Hexafluoride Microbubbles Injection).

We consider this a complete, class 2 response to our November 27, 2013 action letter. Therefore, the user fee goal date is October 11, 2014.

If you have any questions, call Frank Lutterodt Regulatory Project Manager, at (301) 796-4251.

Sincerely,

*{See appended electronic signature page}*

Frank Lutterodt, M.S.
Regulatory Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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FRANK A LUTTERODT
04/21/2014

Record of Telephone Conversation
NDA 203-684
Sponsor: Bracco
Today's date: November 20, 2013

Speakers:

**Bracco:**
Alberto Spinazzi, M.D., Sr. Vice President, Worldwide Medical & Regulatory Affairs Bracco
Andrew Betournay, Head, Corporate Regulatory Affairs, Bracco Italy
Melanie Benson, Director, US Regulatory Affairs BDI
Cristiana Colli, Corporate Quality Management, Bracco Italy
François Tranquart, General Manager, Bracco Suisse SA
Vincent Letondal, Site Director, Bracco Suisse SA
Nicolas Follonier, Manager, Production, Bracco Suisse SA
Paolo Mornata, Director, Finished Goods Operation Bracco Italy

**FDA:**

Shaw Chen, M.D., Deputy Office Director, ODEIV
Libero Marzella, M.D., Ph.D. Acting Division Director, DMIP
Alexander Gorovets, M.D., Clinical Team Leader, DMIP
Milagros Salazar-Driver, Ph.D., CMC Reviewer, DNDQA III
Danae Christodoulou, Ph.D., Acting Branch Chief, ONDQA
Eldon Leutzinger, Ph.D., CMC Lead, DNDQA III
Gene Williams, Ph.D., Clinical Pharmacology Team Leader, DCP5
Merideth Rose, Regulatory Operations, OC
Jagjit Grewal, M.P.H., Acting Associate Director of Regulatory Affairs, ODEIV
Frank Lutterodt, M.S., Regulatory Project Manager, DMIP

FDA called Bracco to provide a status update regarding the review for Lumason/NDA 203-684. FDA explained that changes, (b) (4) are not reflected in the batch record provided in module 2 of their resubmission. More importantly, the data submitted thus far is not adequate to verify implementation of changes since the last review cycle.

Satisfactory resolution of these deficiencies and a re-inspection is required before this application may be approved. FDA informed Bracco that a communication will be issued by the end of the week.

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/s/

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FRANK A LUTTERODT
11/27/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203-684
IND 046, 958

**INFORMATION REQUEST**

Bracco Diagnostics Inc.
Attention: Melanie Benson
Director, U.S. Regulatory Operations
259 Prospect Plains RD.
Monroe Township, NJ 08831

Dear Ms. Benson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lumason (Sulfur Hexafluoride Microbubbles Injection).

We acknowledge your May 31, 2013 submission, containing a Pediatric Development Plan to study the efficacy and safety of Lumason echocardiography for left ventricular endocardial border delineation among 92 patients aged 9-17 years. We have completed our review of the submission, and have the following comments.

To comply with the PSP Guidance, we request that you provide:

1. Success criteria for the endocardial border delineation (EBD) score difference between contrast and non-contrast echocardiography and timing of endpoint assessment.

2. Success criteria for the ability of Lumason to opacify the left ventricular chamber.

3. A statistical approach (e.g., statement of null and alternative hypotheses, sample size/power justification) for these two endpoints.

4. Stopping criteria for the study and a plan for reassessment of safety if serious or severe adverse reactions possibly related to the drug are identified.

5. A secondary endpoint to assess the percentage of patients converting from sub-optimal to adequate imaging after contrast administration.

6. A revised study title (if needed) to reflect the statistically justified number of study patients.

Please submit your revised PSP to your IND 046,958.

If you have any questions, call Frank Lutterodt, Regulatory Project Manager, at (301) 796-4251.

Sincerely,

*{See appended electronic signature page}*

Libero Marzella, M.D., Ph.D.
Acting Director
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

CC: IND046, 958

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/s/

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LIBERO L MARZELLA
11/27/2013

**DEPARTMENT OF HEALTH & HUMAN SERVICES**

**Food and Drug Administration**
**Silver Spring, MD 20993**

NDA 203684

**PROPRIETARY NAME REQUEST**
**CONDITIONALLY ACCEPTABLE**

Bracco Diagnostics Inc.
259 Prospect Plains Road Bldg. H
Monroe Township, NJ 08831

Attention: Melanie Benson
Director, US Regulatory Operations

Dear Ms. Benson:

Please refer to your New Drug Application (NDA) dated December 21, 2011, received December 21, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sulfur Hexafluoride Lipid Microsphere, Injectable Suspension, 1.5 to 5.6 x $10^8$ microspheres/mL.

We also refer to your September 12, 2013, correspondence, received September 13, 2013, requesting review of your proposed proprietary name, Lumason. We have completed our review of the proposed proprietary name, Lumason and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your December 21, 2011 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Teena Thomas, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0549. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Frank Lutterodt at (301) 796-4251.

Sincerely,

*{See appended electronic signature page}*

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

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CAROL A HOLQUIST
11/04/2013

**From:** Lutterodt, Frank A
**To:** Benson Melanie (Melanie.Benson@diag.bracco.com)
**Subject:** Draft Labeling for Sulfur Hexafluoride Microbubbles
**Date:** Friday, November 01, 2013 4:49:00 PM
**Attachments:** draft-labeling-text-redline Nov 2013 SKFLfin (2).doc

Bracco Diagnostics Inc.
Attention: Melanie Benson
Director, US Regulatory Affairs
259 Prospect Plains RD BLDG H
Monroe Township, NJ, 08831

Dear Ms. Benson:

Please find FDA edits to the Prescribing Information resubmitted by Bracco Diagnostics on March 31, 2013. Please examine these and resubmit the revised labeling as an amendment to your NDA. The edited sections are in track changes including a comment within the labeling suggesting that you reduce the size of the images in section 2.2. We hope to minimize typo/format errors.

If you have any questions, call me at 301-796-4251.

Sincerely,

Frank

Frank Lutterodt, M.S. ¦ Regulatory Health Project Manager ¦ Division of Medical Imaging Products
Office of Drug Evaluation IV ¦ Center for Drug Evaluation and Research ¦ Food and Drug Administration
10903 New Hampshire Avenue, Room 5483 ¦ Silver Spring, MD 20993
Phone: (301) 796.4251 • Fax: (301) 796.9849 ¦ Frank.Lutterodt@fda.hhs.gov

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/s/

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FRANK A LUTTERODT
11/04/2013

**PeRC PREA Subcommittee Meeting Minutes**
**October 16, 2013**

**PeRC Members Attending:**
Lynne Yao
Robert Skip Nelson
Karen Davis-Bruno (Did not review Sulfur Hexafluride)
Rosemary Addy
Patricia Dinndorf
Julia Pinto
William J. Rodriguez
Peter Starke
Wiley Chambers
Gilbert Burckart
Daiva Shetty (Did not review Sulfur Hexafluride)
Barbara Buch
Martha Nguyen
Jane Inglese
Kevin Krudys
Lisa Kammerman (Did not review (b) (4) Sulfur Hexafluride)
Gregory Reaman
Ruthianna Davi
Rachel Witten
Maura O'Leary
Tom Smith
George Greeley

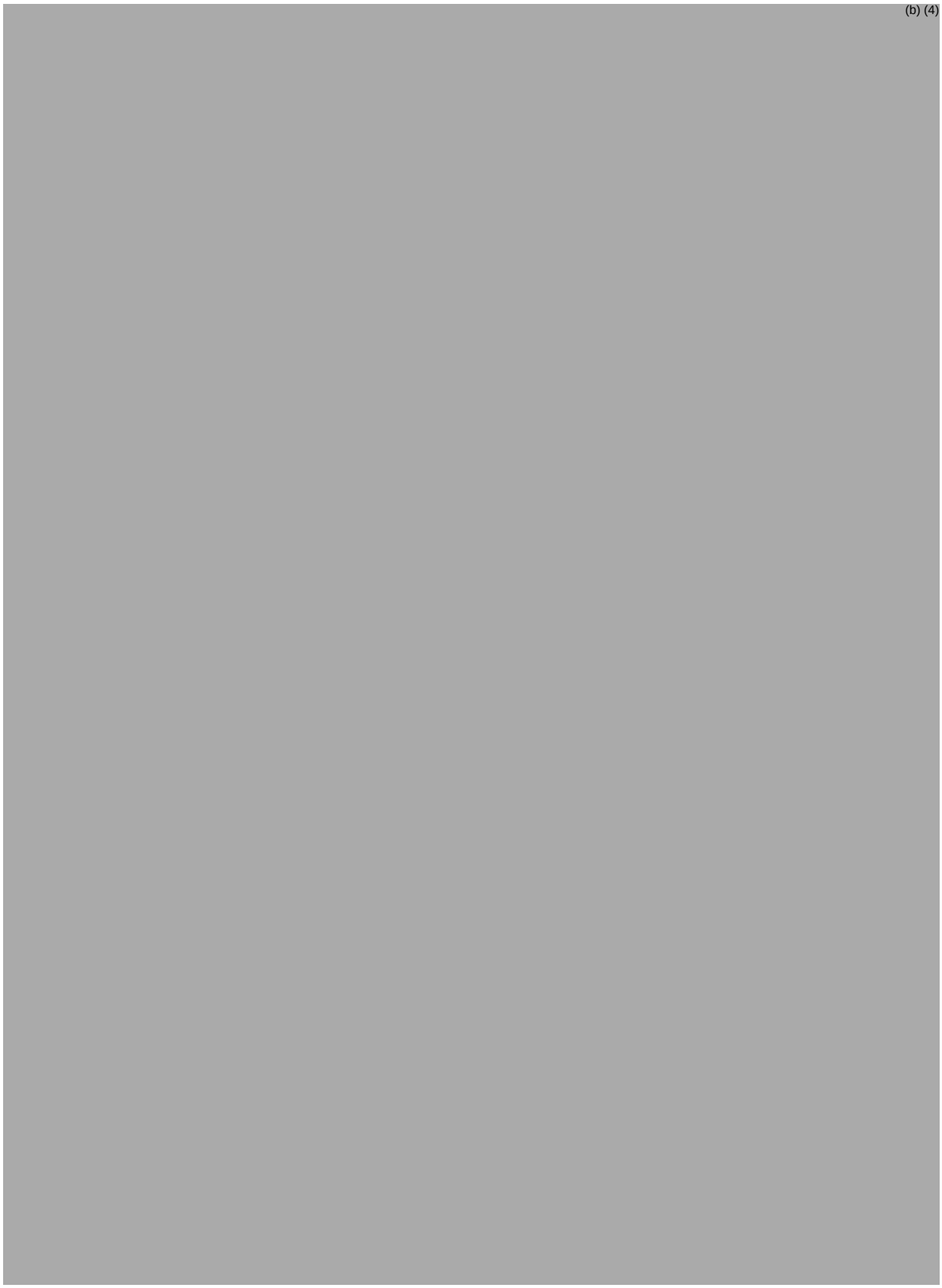
**Guests Attending:**

| | |
|---|---|
| Maura Oleary (CBER) | Ethan Hausman (PMHS) |
| Courtney Suggs (OCP) | Laurie Muldowney (DGIEP) |
| Nichella Simms (PMHS) | Anil Rajpal (DGIEP) |
| Erica Radden (PMHS) | Sushanta Chakder (DGIEP) |
| Kevin Bugin (DGIEP) | Banu Karimi-Shah (DPARP) |
| Donna Snyder (PMHS) | Erika Torjusen (DPARP) |
| Fariba Izabi (DAIP) | Hala Shamuddin (DAIP) |
| Miriam Dinatale (PMHS) | Lawren Slate (OCP) |
| Shivani Gandi (OCP) | Norman Hershkowitz (DNP) |
| Su-Lin Sun (DNP) | Bei Yu (OCP) |
| Angela Men (OCP) | Atul Bhattaram (OCP) |

**Agenda**

| | | | |
|---|---|---|---|
| 11:05 | NDA | (b) (4) | |
| 11:30 | NDA | 203684 | Sulfur Hexafluride (Partial Waiver/Deferral/Plan) |
| | NDA | (b) (4) | |

(b) (4)




**Sulfur Hexafluride Partial Waiver/Deferral/Plan**

- NDA 203684, Sulfur Hexafluride, injection seeks marketing approval for use in echocardiography in patients with suboptimal echocardiograms to obtain left ventricular opacification and improve endocardial border delineation
- The NDA was submitted on May 31, 2013 and has a PDUFA goal date of November 30, 2013.
- The product triggers PREA as a new: active ingredient, indication, dosage form, dosing regimen, and route of administration.
- A waiver is being requested for pediatric patients aged birth to less than 9 years because studies would be impossible or highly impractical.
- *Division justification for waiver*: (b) (4) -enhanced echocardiography for left ventricular opacification and endocardial border delineation has too few pediatric patients under age 9 years and has extremely limited applicability in that pediatric population
- A deferral is being requested for pediatric patients ages 9 to 17 years for because the product is ready for approval in adults.
- The PeRC agreed to the proposed timelines for the deferred studies.

*PeRC Recommendations:*

- The PeRC agreed with the Division to grant a partial waiver in pediatric patients ages birth to 8 years for because studies are impossible or highly impractical.
- The PeRC agreed with the Division to grant a deferral for pediatric patients ages 9 to 17 years because the product is ready for approval in adults.

Additional PeRC Recommendation:

- The PeRC recommends that the Division remove (b) (4) from the title of the trial. The sponsor will need to submit a full protocol and full statistical analysis plan with justification for the sample size.
- PeRC clarified that both indications have to be included in Section 8.4 (noted on page 6, 11, 14 and 15 of the template)
- Both indications must be included in the PREA PMR at the time of approval.
- PeRC would recommend under "Exclusion Criteria" that the Division remove the exclusion of (b) (4)

(b) (4)


(b) (4)

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/s/

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GEORGE E GREELEY
10/29/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 203684

**PROPRIETARY NAME REQUEST**
**UNACCEPTABLE**

Bracco Diagnostics Inc.
259 Prospect Plains Road Building H
Monroe Township, NJ 08831

Attention: Melanie Benson
Director, US Regulatory Operations

Dear Ms. Benson:

Please refer to your New Drug Application (NDA) dated December 21, 2011, received December 21, 2011, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Sulfur Hexafluoride Lipid Microspheres Kit for Preparation of Injectable Suspension.

We also refer to:

- FDA Complete Response Letter dated October 19, 2012
- Your resubmission of your NDA dated, May 31, 2013, which included a Request for Proprietary Name review of your proposed proprietary name (b) (4)

We have completed our review of this proposed proprietary name (b) (4) and have concluded that this name is unacceptable for the following reasons:

(b) (4)

(b) (4)

We note that you have proposed an alternate proprietary name in your submission dated May 31, 2013. In order to initiate the review of the alternate proprietary name, Lumason, submit a new complete request for proprietary name review. The review of this alternate name will not be initiated until the new submission is received.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Sandra Rimmel, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2445. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager Frank Lutterodt at (301) 796-4251.

Sincerely,

*{See appended electronic signature page}*

Kellie Taylor, PharmD, MPH
Deputy Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

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KELLIE A TAYLOR
08/26/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203-684 **INFORMATION REQUEST**

Bracco Diagnostics Inc.
Attention: Melanie Benson
Director, U.S. Regulatory Operations
259 Prospect Plains RD.
Monroe Township, NJ 08831

Dear Ms. Benson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sulfur Hexafluoride Lipid Microsphere for Injectable Suspension.

We also refer to your May 31, 2013 resubmission, containing responses to the following deficiencies outlined in the October 19, 2012 "Complete Response" letter:

- Facilities Inspections and CMC Modules,
- Related Apparatus,
- Labeling and Safety Update,
- Proprietary Name and
- Partial Pediatric Studies Waiver Request.

We are reviewing your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

## CMC MODULES

There is no evidence that Module 2 and Module 3 have been revised to show changes due to correction of inspectional deficiencies. Therefore, we request the following additional information in order to consider the resubmission complete for review:

1. Provide marked and clean copies of Module 2 and Module 3 to have a track of the changes of all manufacturing procedures, controls and testing due to the responses and resolution of the inspectional deficiencies.

2. In order to summarize changes in the production process (i.e., batch size, manufacturing formula, reaction conditions, IPCs, etc.), a table with a list of all critical manufacturing procedures, equipment and controls that are known to have an impact on the quality and efficacy of the lyophilized and reconstituted products would expected. The table should

include reference to the sections in Module 2 and 3 that were changed and a brief statement to explain the reason for the change. This tabular information may be included in the pharmaceutical development section.

3. If revised specifications of [redacted] (b) (4)

4. After the production and control processes have been optimized and accepted by the investigator and the office of compliance consistent with a production process is under control, a revised English translated version of the master batch record (blank and executed) should be reported to the NDA as part of Module 3-Regional Information.

**RELATED APPARATUS**

5. Our records indicate the Mini-Spike [redacted] (b) (4)

If you have any questions, call Frank Lutterodt, Regulatory Project Manager, at (301) 796-4251.

Sincerely,

*{See appended electronic signature page}*

Libero Marzella, M.D., Ph.D.
Acting Director
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

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LIBERO L MARZELLA
07/25/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203-684

**ACKNOWLEDGE –**
**CLASS 2 RESPONSE**

Bracco Diagnostics Inc.
Attention: Melanie Benson
Director, U.S. Regulatory Operations
259 Prospect Plains RD.
Monroe Township, NJ 08831

Dear Ms. Benson:

We acknowledge receipt on May 31, 2013, of your May 31, 2013, resubmission of your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sulfur Hexafluoride Microbubbles Injection.

We consider this a complete, class 2 response to our October 19, 2013, action letter. Therefore, the user fee goal date is November 29, 2013.

If you have any questions, call Frank Lutterodt Regulatory Project Manager, at (301) 796-4251.

Sincerely,

*{See appended electronic signature page}*

Kyong Kang, Pharm.D.
Chief, Project Management Staff
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

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KYONG A KANG
06/07/2013

Record of Telephone Conversation

NDA 203-684

Sponsor: Bracco

Today's date: October 3, 2012

Speakers:

Bracco:
Alberto Spinazzi, M.D., Sr. Vice President, Group Medical and Regulatory Affairs
Melanie Benson, B.A., Director, Head US Regulatory
Usha Halemane, Head, Corporate Medical Biometrics & Medical Writing
Luigia Storto, M.D., Executive Director, X-Ray Medical Affairs
Marie Morris, Head, Corporate Clinical Research
Andrew Betournay, Group Regulatory Affairs
Ann Garvey, Senior Manager, Medical Writing
Alexandra Davies, C.O. Medical Communications
Melda Dolan, M.D., Sr. Director, Medical Planning & Management Ultrasound Programs
William Gray, Sr. Director Regulatory Affairs North and Latin America

FDA:
Dwaine Rieves, M.D., Division Director, DMIP
Scheldon Kress, M.D., Clinical Reviewer, DMIP
Milagros Salazar-Driver, Ph.D., CMC Reviewer, DNDQA III
Eldon Leutzinger, Ph.D., CMC Lead, DNDQA III
Mary Brooks, RN, BSN, M.S., Device Reviewer, GHDB, CDRH
Mahesh Ramanadham, Regulatory Operations, OC
Merideth Rose, Regulatory Operations, OC
Derek Smith, Ph.D., Chemist, OC
Steven Hertz, Consumer Safety Officer, OC
Frank Lutterodt, M.S., Regulatory Project Manager, DMIP

FDA called Bracco to provide a status update regarding the review for Sonovue/NDA 203-684. FDA outlined three major deficiencies that will need to be resolved before the team can recommend a favorable finding for the application, as follows:

1) Facility inspectional issues for the Bracco Suisse manufacturing site;
2) Transfer device/510k information (a component within the kit);
3) Labeling.

FDA informed Bracco that this telephone call was to let them know that deficiencies have been identified such that they are not surprised by FDA's response at the end of the

review cycle. FDA noted that draft package insert labeling is anticipated to be provided within the final review finding.

Bracco asked Office of Compliance representatives about the status of their response to the manufacturing site deficiencies (they responded in May, 2012). FDA noted that this response is under review and communication will be provided to Bracco via a parallel pathway (i.e., not within the final NDA review cycle document). Bracco thanked FDA for the telephone call.

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/s/

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FRANK A LUTTERODT
10/03/2012

RAFEL D RIEVES
10/03/2012

**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 203684

**PROPRIETARY NAME REQUEST**
**UNACCEPTABLE**

Bracco Diagnostics Inc.
107 College Road East
Princeton, NJ 08540

Attention: William Gray, MS
Sr. Director, Regulatory Affairs

Dear Mr. Gray:

Please refer to your New Drug Application (NDA) dated December 21, 2011, received December 21, 2011, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Sulfur Hexafluoride Injectable Suspension, 8 microliters/mL.

We also refer to your June 18, 2012, correspondence, received June 19, 2012, requesting reconsideration of your proposed proprietary name, SonoVue. We have completed our review of the information submitted as part of your request for reconsideration and have concluded that this information is insufficient to support the use of the proposed name for this product. Therefore, we continue to object to the use of this proposed proprietary name.

(b) (4)

(b) (4)

In summary, based on the information provided in support of the reconsideration of the name, Sonovue, we do not agree that the name Sonovue is acceptable. We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review. (See the Guidance for Industry, *Complete Submission for the Evaluation of Proprietary Names,* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf and "PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012".)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Sandra Griffith, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2445. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager Frank Lutterodt at (301) 796-4251.

Sincerely,

*{See appended electronic signature page}*

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

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CAROL A HOLQUIST
09/17/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203-684

**INFORMATION REQUEST**

Bracco Diagnostics Inc.
Attention: William Gray, M.S.
Director, US Regulatory Affairs
107 College Road East
Princeton, NJ 08540

Dear Mr. Gray:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SonoVue™(Sulfur Hexafluoride) Microbubbles Injection.

We have the following comments and information requests regarding your vial, carton and shipper labels:

**A. Vial Label**

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

8. The label of the Single dose vial FCE0000-SONOVUE-25MG must have the statement of composition such as:
   Each vial contains a sterile, nonpyrogenic, lyophilized formulation of 24.56 mg polyethylene glycol 4000, 0.19 mg of 1,2-Distearoyl-phosphatidylcholine, 0.19 mg of 1,2-Dipalmitoyl-phosphatidylglycerol sodium and 0.04 mg of palmitic acid. Vial contents are sealed under sulfur hexafluoride at time of manufacture.

   Upon reconstitution, the injectable suspension contains 1.5 to 5.6 $x10^8$ microspheres/mL with a pH of 4.5 to 7.5.

**B. Kit Carton Labeling**

1. See comment A.1.through A.5. and revise carton labeling accordingly

**C. Shipper Carton Labeling**

1. See comment A.1 through A.5.

**D. Syringe Label for Sodium Chloride Injection, USP (diluent)**

1. Revise the Sodium Chloride Syringe Label to state diluent after Sodium Chloride Injection. The label should read, "Sodium Chloride Injection, USP, 0.9% Sodium Chloride (DILUENT)…" to clarify the syringe does not contain any active ingredient.

We request a prompt written response in order to continue our evaluation of your NDA.

If you have any questions, call me at (301) 796-4251.

Sincerely,

*{See appended electronic signature page}*

Frank Lutterodt, M.S.
Regulatory Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

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FRANK A LUTTERODT
08/23/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203-684

**INFORMATION REQUEST**

Bracco Diagnostics Inc.
Attention: William Gray, M.S.
Director, US Regulatory Affairs
107 College Road East
Princeton, NJ 08540

Dear Mr. Gray:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SonoVue™(Sulfur Hexafluoride) Microbubbles Injection.

As an aid to our review of the effect of Sonovue on QT, the clinical pharmacology reviewer requests the following. The items are listed in order of importance for accomplishing the review. To expedite our review, we encourage that each item be submitted as it is available, rather than waiting until all items are available and bundling into a single submission.

1. Completion of the following "Highlights of Clinical Pharmacology Table." We understand that information for selected items may be inapplicable to your intravenously administered drug product.

**Highlights of Clinical Pharmacology Table**

| | | |
|---|---|---|
| Therapeutic dose | Include maximum proposed clinical dosing regimen | |
| Maximum tolerated dose | Include if studied or NOAEL dose | |
| Principal adverse events | Include most common adverse events; dose limiting adverse events | |
| Maximum dose tested | Single Dose | Specify dose |
| | Multiple Dose | Specify dosing interval and duration |
| Exposures Achieved at Maximum Tested Dose | Single Dose | Mean (%CV) Cmax and AUC |
| | Multiple Dose | Mean (%CV) Cmax and AUC |
| Range of linear PK | Specify dosing regimen | |
| Accumulation at steady state | Mean (%CV); specify dosing regimen | |
| Metabolites | Include listing of all metabolites and activity | |
| Absorption | Absolute/Relative Bioavailability | Mean (%CV) |
| | Tmax | • Median (range) for parent |

| | | |
|---|---|---|
| | | • Median (range) for metabolites |
| Distribution | Vd/F or Vd | Mean (%CV) |
| | % bound | Mean (%CV) |
| Elimination | Route | • Primary route; percent dose eliminated<br>• Other routes |
| | Terminal t½ | • Mean (%CV) for parent<br>• Mean (%CV) for metabolites |
| | CL/F or CL | Mean (%CV) |
| Intrinsic Factors | Age | Specify mean changes in Cmax and AUC |
| | Sex | Specify mean changes in Cmax and AUC |
| | Race | Specify mean changes in Cmax and AUC |
| | Hepatic & Renal Impairment | Specify mean changes in Cmax and AUC |
| Extrinsic Factors | Drug interactions | Include listing of studied DDI studies with mean changes in Cmax and AUC |
| | Food Effects | Specify mean changes in Cmax and AUC and meal type (i.e., high-fat, standard, low-fat) |
| Expected High Clinical Exposure Scenario | Describe worst case scenario and expected fold-change in Cmax and AUC. The increase in exposure should be covered by the supra-therapeutic dose. | |

2. A single dataset containing all of the raw QT. The file should include (each item is a column):
   A) Clinical study number
   B) Subject ID
   C) Dose (nominal)
   D) Dose (actual)
   E) Time (nominal time pre- or post-dose)
   F) Time (actual time pre- or post-dose)
   G) Actual QT (units of ms)
   H) QTc (units of ms)
   I) Categorical variable stating correction method (e.g., Fredricia's)
   J) Whether subject was sampled for PK
   K) Separate columns for each subject's demographic data (sex, weight, age) and other variables potentially influencing QT (as available -- cardiac risk factors, concomitant medications, other factors identified by Bracco) should be included and be repeated for each row of the dataset
   L) (and subsequent) Other information as Bracco desires to include.

3. A single dataset containing all of the raw concentration data for subjects with QT data that also had PK analyses in the submission. The file should include (each item is a column):
   A) Clinical study number
   B) Subject ID
   C) Dose (nominal)
   D) Dose (actual)
   E) Time (nominal time pre- or post-dose)
   F) Time (actual time pre- or post-dose)
   G) Conc (units of mass/volume)
   H) Separate columns for each subject's demographic data (sex, weight, age) and other variables potentially influencing PK (as available -- creatinine clearance, liver chemistries, disease states, other factors identified by Bracco) should be included and be repeated for each row of the dataset
   I) (and subsequent) Other information as Bracco desires to include.

4. A single dataset containing all of the raw data from the analytical runs for all samples contributing to the PK analysis in the prior item. The file should include (each item is a column):
   A) Clinical study number
   B) Calendar date of analysis of the sample ("sample" includes blanks, standards, QCs -- all determinations included in the analytical run)
   C) Clock time of analysis of the sample
   D) Categorical variable describing sample type -- blank, standard, QC, subject data, re-analysis, dilution
   E) For subject data only (column is empty for non-subject samples) -- subject ID, nominal post-dose sample time, actual post-dose sample time (these could be split into separate columns if desired)
   F) For subject data only (column is empty for non-subject samples and for samples that are not dilutions) -- the degree (x-fold) of dilution
   G) (and subsequent) Other information as Bracco desires to include.

If you have any questions, call me at (301) 796-4251.

Sincerely,

*{See appended electronic signature page}*

Frank Lutterodt, M.S.
Regulatory Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

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FRANK A LUTTERODT
06/19/2012

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 203684

**PROPRIETARY NAME REQUEST**
**UNACCEPTABLE**

Bracco Diagnostics Inc.
107 College Road East
Princeton, NJ 08540

Attention: William Gray, MS
Sr. Director, Regulatory Affairs

Dear Mr. Gray:

Please refer to your New Drug Application (NDA) dated December 21, 2011, received December 21, 2011, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Sulfur Hexafluoride Injectable Suspension, 8 microliters/mL.

We also refer to your January 27, 2012, correspondence, received January 27, 2012, requesting review of your proposed proprietary name, SonoVue. We have completed our review of the proposed proprietary name, SonoVue, and have concluded that it is unacceptable for the following reasons:

(b) (4)

[redacted]

1 Page has been Withheld in Full as b4 (CCI/TS) immediately following this page.

[redacted] (b) (4)

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review. (See the Guidance for Industry, *Complete Submission for the Evaluation of Proprietary Names,* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf and "PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012".)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Sandra Griffith, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2445. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager Frank Lutterodt at (301) 796-4251.

Sincerely,

*{See appended electronic signature page}*

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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CAROL A HOLQUIST
04/25/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203-684

**INFORMATION REQUEST**

Bracco Diagnostics Inc.
Attention: William Gray, M.S.
Director, US Regulatory Affairs
107 College Road East
Princeton, NJ 08540

Dear Mr. Gray:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SonoVue™(Sulfur Hexafluoride) Microbubbles Injection.

We have determined that the lipid components (shell components of microsphere) are part of the drug substance (whole microsphere). Therefore, we would need to inspect the manufacturing sites of the lipids for compliance with CGMPs.

Please submit a statement of readiness for inspection to the following sites together with their respective CFN or FEI numbers and contact person's information:

(b) (4)

We request a prompt written response in order to continue our evaluation of your NDA.

If you have any questions, call me at (301) 796-4251.

Sincerely,

*{See appended electronic signature page}*

Frank Lutterodt, M.S.
Regulatory Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

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FRANK A LUTTERODT

03/23/2012

_____

From: Lutterodt, Frank A
Sent: Friday, March 23, 2012 8:45 AM
To: 'Gray Bill'
Subject: SonoVue NDA 203-684- New Inspection sites

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203-684

**FILING COMMUNICATION**

Bracco Diagnostics Inc.
Attention: Melanie Benson
Director, US Regulatory Affairs
107 College Road East
Princeton, NJ 08540

Dear Ms. Benson:

Please refer to your New Drug Application (NDA) dated December 20, 2011, received December 21, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for SonoVue™(Sulfur Hexafluoride) Microbubbles Injection.

We also refer to your amendments dated February 9 and 27, 2012.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is October 21, 2012.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by September 2, 2012.

During our filing review of your application, we identified the following potential review issues:

**Chemistry Manufacturing and Controls (CMC)**

1. The drug substance, API, in SonoVue™ product is the microsphere which is composed of the gas core and lipid shell. Therefore, the drug substance sections, 2.3.S and 3.2.S, of the

application should describe the nature of this material and include full CMC information for each of the microsphere components.

2. Item 1 above should be also applied to the drug product. Therefore, the drug product section should be revised to comply with USP nomenclature and other currently approved product of the same class, as follows:

   SonoVue™ (Sulfur Hexafluoride Lipid Microsphere) for Injectable Suspension

   We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

We request that you submit the following information:

3. A revised drug product section 2.3.P and 3.2.P that includes the concentration of the lipid components per mL as part of the drug product strength.

4. A revised draft labeling of the product according to the above comments and revisions.

5. The actual container labels and carton labeling that you intend to market. Your current submission only displays the text of the labels and labeling. We require the actual labels and labeling so that we can evaluate the color contrasts, label size, placement of information on the labels, and other aspects of the label.

**PROMOTIONAL MATERIAL**

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

**REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Pediatric studies conducted under the terms of section 505B of the Federal Food, Drug, and Cosmetic Act (the Act) may also qualify for pediatric exclusivity under the terms of section 505A of the Act. If you wish to qualify for pediatric exclusivity please consult the Division of Medical Imaging Products. Please note that satisfaction of the requirements in section 505B of the Act alone may not qualify you for pediatric exclusivity under 505A of the Act.

(b) (4)

If you have any questions, call Frank Lutterodt, Regulatory Project Manager, at (301) 796-4251.

Sincerely,

*{See appended electronic signature page}*

Rafel Dwaine Rieves, M.D.
Director
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

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RAFEL D RIEVES
03/02/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203-684

**NDA ACKNOWLEDGMENT**

Bracco Diagnostics Inc.
Attention: Melanie Benson, M.S.
Director, US Regulatory Affairs
107 College Road East
Princeton, NJ 08540

Dear Ms. Benson:

We have received your New Drug Application (NDA) under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: SonoVue™(Sulfur Hexafluoride) Microbubbles Injection

Date of Application: December 20, 2011

Date of Receipt: December 21, 2011

Our Reference Number: NDA 203-684

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 19, 2012, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

**FDAAA TITLE VIII RESPONSIBILITIES**

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Medical Imaging Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

If you have any questions, call me at (301) 796-4251.

Sincerely,

*{See appended electronic signature page}*

Frank Lutterodt, M.S.
Regulatory Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

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FRANK A LUTTERODT
01/04/2012