CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203684Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203684

COMPLETE RESPONSE

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

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 Lumason (sulfur hexafluoride lipid microspheres) Kit for Preparation of Injectable Suspension.

We acknowledge receipt of your amendments dated January 27, February 9 and 27, March 2, April 19 and 26, May 10, June 19, July 23, September 13, December 7 and 14, 2012; January 7, May 31, August 19, September 13 and 25, and November 12, 2013.

The May 31, 2013, submission constituted a complete response to our October 19, 2012, action letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

FACILITY INSPECTIONS

1. During an inspection of the Bracco Suisse manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. The changes, such as manufacturing temperatures, that have been made to address deficiencies with the PEG4000 are not reflected in the batch record provided in module 2 of your application. Satisfactory resolution of these deficiencies and a re-inspection is required before this application may be approved. Please also refer to our Request for Additional Information dated November 19, 2013.

   Your application has not been updated to include the critical control process parameters to show that the manufacturing process and product are under control. You need to revise Module 2 and Module 3 of the application to reflect changes in the manufacturing and controls that have been incorporated to address the inspection findings to support resolution of past product failures.

Amend the chemistry, manufacturing, and controls sections in Module 2 and Module 3 of your application as follows:

a. Add the specification for the Appearance test of the Lumason powder product in the vial before reconstitution, referencing the control for the absence of [redacted] or presence of [redacted] Consider for example, an acceptance criteria of [redacted] Include this revision in section M3.2.P.5.1 (and corresponding M2 section) of your application.

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

c. Update section M3.2.P.3.3 (and corresponding M2 section) with a flow diagram of all in-process controls, particularly the ones considered critical as listed in your submission dated August 19, 2013.

d. Update section M3.2.P.3.3-Description of the Manufacturing Process (and corresponding M2 section) to describe the holding time and temperature used during the critical steps of the manufacturing process such as the [redacted] filling and loading, lyophilization, and visual inspection.

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

f. Summarize the resolution of inspectional deficiencies and describe the changes you have implemented after the root cause investigation of product/process failures. Explain how the changes are associated with a resolution of the issues with quality control of the end product.

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

h. Provide a copy of the Master Batch Record with the recommended and accepted changes that yield a consistent process and product and that are acceptable to the Office of Compliance for the resolution of inspectional deficiencies.

i. Provide the control release testing data on the lyophilized vial before reconstitution and after reconstitution products for lot(s) sample(s) manufactured with the implemented changes. These changes include ingredient control for PEG4000, [redacted] optimal time and temperatures for holding [redacted] and controls for all in-process critical product

quality attributes including the new test for [redacted] (b) (4) The control data should include all testing attributes for both the lyophilized and reconstituted products as described in section 3.2.P.5.1 of your application.

j. Provide control release testing data on the lyophilized vial before reconstitution and after reconstitution products on samples failing the [redacted] (b) (4) test. The control data should include all testing attributes for both lyophilized and reconstituted products as described in section 3.2.P.5.1 of your application.

k. [redacted] (b) (4) Alternatively, the process conditions (e.g. temperature, holding times) might not be fully optimized to obtain the desired quality of the final product. Please comment.

LABELING

2. Submit draft labeling that incorporates revisions in the attached labeling. In addition, submit updated 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.

   To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should include annotations that support any proposed changes.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
   - Present tabulations of the new safety data combined with the original NDA data.
   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.

- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry, "Formal Meetings Between the FDA and Sponsors or Applicants," May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

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

Sincerely,

{See appended electronic signature page}

Shaw T. Chen, M.D., Ph.D.
Deputy Director
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

ENCLOSURE:
Labeling

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

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

/s/

SHAW T CHEN
11/27/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203-684

COMPLETE RESPONSE

Bracco Diagnostics Inc.
Attention: William B. Gray, M.S.
Senior Director, North and Latin Americas Regulatory Affairs
107 College Road East
Princeton, NJ 08540

Dear Mr. Gray:

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 lipid microspheres) Kit for Preparation of Injectable Suspension.

We acknowledge receipt of your amendments dated February 27, March 2, April 20 and 26, May 11, June 19, July 24, and September 13, 2012.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues. You must satisfactorily address all the deficiencies and requests listed below before this application may be approved.

FACILITY INSPECTIONS

1. During an inspection of the Bracco Suisse manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. In addition to the items listed below, satisfactory resolution of inspectional deficiencies is required before this application may be approved. Additionally, amend the chemistry, manufacturing and controls (CMC) sections in Module 2 and Module 3 of your application to contain applicable information if resolution of the inspectional deficiencies requires any new manufacturing and control procedures.

RELATED APPARATUS

2. Your drug is to be supplied within a package that contains the drug vial, a pre-filled glass syringe with an attached (b) (4) referred to as (b) (4) and a transfer device (to attach the pre-filled syringe to the drug vial). The transfer device is referred to as the "Mini-Spike (b) (4)." Your application contained a letter of authorization from B. Braun Melsungen AG, the manufacturer of the Mini-Spike (b) (4). This letter authorized FDA

to examine 510(k) number [redacted] in support of the Mini-Spike [redacted] model. We examined this 510(k) application and determined the model known as Mini-Spike [redacted] is not part of [redacted] submission clearance. We have determined that Mini-Spike [redacted] is a model number available in the European market and not available for distribution within the USA.

a. Provide a document that describes the fundamental differences between the Mini-Spike [redacted] model and the other transfer device models cleared under [redacted] Include sufficient information to allow us to verify the quality, composition and construct of the Mini-Spike [redacted]

b. Within your response, describe any [redacted] within the Mini-Spike [redacted] Specifically, does the device contain a [redacted]?

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

3. The [redacted] that attaches to the glass syringe referred to as [redacted] does not have a reference premarket 510(k) clearance number. Please clarify whether or not the device has a 510(k) clearance. If the device is to be reviewed under the NDA, the following information will be necessary to complete the review:

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

   b. The design specifications,

   c. A biocompatibility assessment of the final finished product [redacted] Please refer to ISO 10993-1, Biological evaluation of medical devices — Part 1: Evaluation and testing.

   d. Performance testing as outlined in ISO 594-2, [redacted] with [redacted] for syringes, needles and certain other medical equipment — Part 2: Lock fittings.

4. It appears [redacted] the glass syringe to the [redacted] please confirm. If a [redacted] is used, please identify the [redacted] and supply the performance testing used to verify proper [redacted] the glass syringe and [redacted]

LABELING

5. Submit revised draft labeling that incorporates the text within the attached labeling example. If you identify typographical or formatting errors within this labeling example, please correct these errors within your response. Supply information to justify any substantive changes to the labeling text. In addition, submit updated 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.

To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should include annotations that support any proposed changes. For the reason outlined below, the attached labeling uses an "X" as a placeholder for your proposed proprietary drug name.

6. You supplied revised container labels within the September 13, 2012 amendment. We find these labels acceptable and have no requests for revision.

PROPRIETARY NAME

As described in our letter of September 17, 2012, your drug's proposed proprietary name (Sonovue) was unacceptable. If you intend to have a proprietary name for your drug, we recommend that you submit a new request for a proposed proprietary name review.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
   - Present tabulations of the new safety data combined with the original NDA data.
   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

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.

(b) (4)

We acknowledge that published literature suggests the occurrence of suboptimal transthoracic echocardiography is less frequent in pediatric patients than in adults. However, we are concerned that some pediatric patients may benefit from the use of your drug, especially older pediatric patients with suboptimal echocardiograms due to obesity or chest structural deformities. As exemplified by a single-center report that described 20 pediatric patients with suboptimal echocardiograms who had improved images with intravenous contrast (Pediatric Cardiology 2005; 26:413-417), we do not concur with your contention that (b) (4)

Therefore, supply a pediatric plan designed to assess the efficacy and safety of your drug in the pediatric population. You may wish to obtain feasibility data that would allow you to substantiate a contention that a study (or studies) is practical only within a subset of the pediatric population; for example, the data may support an age threshold for study recruitment feasibility. These data may substantiate the design features for a study within the defined pediatric patient population subset and also justify a waiver of studies within the unfeasible subset of patients.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's "Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants," May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

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

Sincerely,

{See appended electronic signature page}

Charles J. Ganley, M.D.
Director
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

ENCLOSURE:
Labeling Example

10 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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

/s/

SUSAN S JOHNSON on behalf of CHARLES J GANLEY
10/19/2012
Signing on behalf of Charles Ganley