DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 19-414/S-014

SUPPLEMENT APPROVAL

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

Dear Ms. Benson:

Please refer to your Supplemental New Drug Application (sNDA) dated December 21, 2011, received December 22, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Cardiogen-82® (Rubidium Rb 82 Generator).

We acknowledge receipt of your amendments dated January 20, 26, and February 3, 2012.

This "Prior Approval" supplemental new drug application proposes revision of the labeling to include:

1. A boxed warning that describes the risk for unintended strontium-82 (Sr-82) and strontium-85 (Sr-85) radiation exposure and the methods to minimize this risk;

2. Dosage and Administration text that:

    a. Details new requisite tests for the quantification of Sr-82 and Sr-85 in CardioGen-82 generator eluates as well as

    b. Provides new generator expiration criteria;

    c. Updates the radiation dosimetry information.

3. A new Warnings and Precautions subsection that describes the risk for unintended Sr-82 and Sr-85 exposure;

4. Minor modification of labeling text to meet Physicians Labeling Rule expectations as well as an updated assay label.

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text. We have the following additional comments:

1. Rubidium Rb 82 chloride injection is administered using a specific type of infusion cart. Portions of the infusion cart operator's manual (Infusion System User's Guide) contain excerpts from the CardioGen-82 labeling. You provided a copy of this manual as a submission to your NDA. Please revise the manual to maintain consistency with the revised CardioGen-82 labeling. We have the following recommendations:

    a. Within the text, always state "activity" when the manual actually refers to activity and "dose" when the manual actually refers to dose. The text seems to intermix these two terms; this intermixing can lead to confusion and potentially jeopardize patient safety.

    b. Replicate in the manual the following sections from the CardioGen-82 labeling:
        i. Full prescribing information boxed warning
        ii. Eluate testing procedures
        iii. Organ dose table.

    c. Provide a warning that the radionuclide detector does not detect strontium breakthrough during an injection.

    d. Regarding Section 4.6, "Purge Modes," we are concerned that purging the system ("Purge –Generator-to-Patient-Line") may increase the risk for administration of excessive radiation to the patient. Please reconsider the text within this section and, if the process is conducive to inadvertent radiation administration to the patient, include a warning or revised text to help minimize the risk. As you refine the cart configuration, we suggest you modify the control panel text on the "purge generator to patient" knob in order to clarify that this purge option applies to the infusion line when it is not contiguous with a patient's intravenous line.

    e. Section 4.7.1 (page 34) Description:
        i. Describe the method for the user to estimate the elution volume for a specific Rb-82 dose, so that a user can enter reasonable values in the elution volume and patient volume thresholds.
        ii. Give tables with examples.

    f. Revise the text to describe the following situation: If the infusion system repetitively terminates the infusion based on excessive patient or elution volumes (above limits) then the user should re-check the volume calculations and verify that the generator has not reached Expiration Limits.

    g. Regarding the Sr-82/85 Breakthrough Worksheet, page 45, please update this text to harmonize with the CardioGen-82 labeling.

2. The revision of the CardioGen-82 labeling followed the detection of excessive exposure of some patients to Sr-82 and Sr-85 coincident with administration of rubidium Rb 82 chloride injection. It appeared unlikely that this excessive radiation exposure posed significant risks to the patients, although exposure to any excessive radiation is undesirable. Investigations disclosed that improper usage of CardioGen-82 generators at clinical sites were responsible for the excessive radiation exposure. The revised labeling describes the importance of compliance with Sr-82 and Sr-85 testing of generator eluates and generator expiration criteria.

3. We understand that you are implementing a generator user certification program and usage monitoring plan to assess safe generator use and compliance with labeling. These procedures should help detect any need for additional labeling revisions or enhancements to the user training program. We anticipate further discussions with you regarding the results of your generator usage monitoring procedures. Please provide a report monthly summarizing the training program activities with an assessment of its effectiveness, and a summary of generator use, with eluate test results

4. We believe technologic improvements could enhance the safety of CardioGen-82. The current generator and infusion cart system does not include a real-time monitoring of radionuclide identity within the generator eluate prior to its infusion into a patient. The system also lacks a robust, real-time mechanism for cessation of the intravenous infusion in the event of excessive Sr-82 and/or Sr-85 content in the generator eluate.

    a. We request you to explore potential technological improvements to the generator and the infusion system in order to minimize the potential for inadvertent Sr-82 and Sr-85 administration to patients. We suggest you plan to provide a summary of a technological improvement proposal within six months following the resumption of CardioGen-82 marketing.

    b. We regard generator and infusion cart technological improvement as a potential mechanism to decrease the intensity of the current Sr-82 and Sr-85 generator eluate testing and to help minimize the risk for medication errors related to the complexity of the Sr-82 and Sr-85 eluate testing. We anticipate further discussions with you regarding your progress in updating the generator eluate infusion technology, including potential consultation with advisors and/or consultants to the FDA.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling text for the package insert, with the

addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. 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 provide appropriate annotations, including supplement number(s) and annual report date(s).

PROMOTIONAL MATERIALS

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

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

ENCLOSURES:
Content of Labeling
Assay Labeling

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

/s/

RAFEL D RIEVES
02/08/2012