



UNITED STATES
NUCLEAR REGULATORY COMMISSION
WASHINGTON, D.C. 20555-0001

(FSME-11-068, July, Other, Cardiogen-82, Rubidium-82 Generator)

July 15, 2011

ALL AGREEMENT STATES, MICHIGAN

NOTIFICATION OF ISSUANCE OF IMPORTANT SAFETY INFORMATION CONCERNING
THE CARDIOGEN-82 RUBIDIUM-82 GENERATOR" (FSME-11-068)

Purpose: To provide the Agreement States with a copy of the information safety notice issued on July 13, 2011, by Braco Diagnostic Incorporated to its customers. The notice was issued to inform users of the CardioGen-82 (rubidium-82 generator) about the importance of performing mandatory strontium-82 and strontium-85 breakthrough checks before using the generator.

Background: Rubidium-82 is a positron emission tomography (PET) myocardial perfusion imaging (MPI) agent. Two individuals who previously underwent Rb-82 PET MPI imaging triggered radiation detectors when travelling to/from the United States. Radiation analyses indicated the presence of Sr-85 and Sr-82.

Discussion: Enclosed for your information is a copy of the important safety information. The U.S. Nuclear Regulatory Commission (NRC) is coordinating with the U.S. Food and Drug Administration (FDA) on this and will keep you informed as more information becomes available. The FDA indicated there are 100 medical facilities using the CardioGen-82 generator.

If you have any questions regarding this communication, please contact me at 301-415-8722 or the individual named below.

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/RA JLuehman for/

Terrence Reis, Acting Director
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and State Agreements
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Enclosure:
Braco Important Safety Information



LIFE FROM INSIDE

July 13, 2011

IMPORTANT SAFETY INFORMATION:

Disseminate to all health care professionals at your facility who perform or supervise PET imaging with CardioGen-82 (Rubidium Rb 82 Generator).

RE: Reports of unexpected radiation exposure to patients: Reminder for *mandatory daily* procedure to check for strontium-82 or strontium-85 (Sr-82, Sr-85) breakthrough when using CardioGen-82[®] (Rubidium Rb 82 Generator)

Dear CardioGen User:

Gamma ray emissions from strontium isotope decay have been detected in two patients who underwent positron-emission tomography (PET) with CardioGen-82[®] (Rubidium Rb 82 Generator). "Strontium breakthrough" can occur with CardioGen-82[®] and necessitates close attention to mandatory daily quality control testing to help minimize radiation risks to patients.

Specifically, two individuals, who had previously undergone Rb-82 PET myocardial perfusion imaging (MPI), were traveling to/from the United States and, when crossing the border, radiation detectors detected gamma radiation emanating from the patients. Analyses of the gamma radiation spectra indicated the presence of Sr-82 in one patient and Sr-82 and Sr-85 in the other. Since Rb-82 has a half-life of 75 seconds, and since these two individuals recounted no other exposure to radioactive substances, the strontium isotope exposure may have originated from the MPI. Both strontium-exposed patients suffered no acute health effects nor required treatment. However, the long-term effects, if any, are not known. Bracco and certain state and federal authorities have undertaken a review of the matter to assess the nature of any CardioGen-82 usage or product problems and the potential exposure of other patients.

In light of the foregoing, Bracco again emphasizes to all CardioGen-82 users the importance of strict adherence to the instructions contained in the prescribing information for CardioGen-82 regarding mandatory daily strontium breakthrough testing (please see section 2.7 of the full prescribing information). As described in user training material, testing for strontium breakthrough may sometimes need to be performed twice daily.

As soon as possible, you should conduct a thorough review of your current CardioGen-82 Quality Control procedures and documentation to ensure that all steps have been, and currently are being followed and documented as outlined in the attached CardioGen-82 Quality Control Procedures. If at any point you have any questions or concerns, you should contact your Bracco Clinical Applications Specialist or Bracco Professional Services department at (800) 257-5181 immediately.

The key components of these instructions are:

- **Use only additive-free Sodium Chloride Injection USP to elute the generator.**
- **Determine the eluate rubidium Rb 82 content and strontium Sr 82 and strontium Sr 85 breakthrough daily prior to the administration of rubidium Rb 82 chloride injection to any patients.**
- **If results from strontium Sr-82/Sr-85 breakthrough testing exceed one-tenth (1/10) of the specification limit (1/10 of specification limit = 0.002 μ Ci Sr-82/mCi Rb-82 or 0.02 μ Ci Sr-85/mCi Rb-82), then perform the Rb-82 assay and Sr-82/Sr-85 breakthrough testing at least twice daily (i.e., the beginning and the middle of day). This additional test should be**

initiated on the day the Sr-82/85 levels exceed 1/10 of the specification limit indicated above and each day thereafter.

- **If Sr-82 or Sr-85 breakthrough exceeds specified limits** (0.02 μCi Sr-82/mCi Rb-82 or 0.2 μCi Sr-85/mCi Rb-82), **discontinue use of the generator and contact Bracco Diagnostics Inc.**

The full prescribing information for CardioGen-82 also states that only additive-free Sodium Chloride Injection USP must be used for eluting the generator. This is because additives (particularly calcium ion $[\text{Ca}^{++}]$, to which Sr^{++} ions are chemically analogous), may cause the release of substantial amounts of $^{82}\text{Sr}^{++}$ and/or $^{85}\text{Sr}^{++}$ ions into the eluate regardless of the age or prior use of the generator.

About CardioGen-82[®] (Rubidium Rb 82 Generator):

CardioGen-82 is a radionuclide generator that produces on-demand, and administers in a controlled fashion through the use of the CardioGen-82[®] Infusion System, rubidium-82 (Rb-82) for positron-emission tomography myocardial perfusion imaging.

The generator contains accelerator-produced strontium-82 (Sr-82), adsorbed on stannic oxide in a lead-shielded column, and provides means for the entrance to and exit from the generator of 0.9% normal saline (NaCl) solution. When 0.9% NaCl solution is passed through the generator at a controlled rate, Na^+ ions from solution are exchanged for $^{82}\text{Rb}^+$ ions generated by the Sr-82 adsorbed to the column, and the $^{82}\text{Rb}^+$ is eluted into solution for patient administration. Due to the chemistry involved, the Sr-82 remains adsorbed to the generator's stannous oxide column.

However, under the conditions of clinical use, "strontium breakthrough" (the release of $^{82}\text{Sr}^{++}$ and also possibly $^{85}\text{Sr}^{++}$ ions by the generator column into solution) can occur, and is allowable under very tightly defined trace level specifications. The possibility of "strontium breakthrough", and the mandatory daily quality control testing that is required to assess for its presence, are addressed in the FDA-approved product labeling for the CardioGen-82, in section 2.7 of the full prescribing information (a.k.a., "package insert"). All CardioGen-82 users are also instructed to perform daily quality control testing, including testing for strontium breakthrough, by the CardioGen-82 Full Prescribing Information, Users' Manual of the CardioGen-82 Infusion System, and personally by their Bracco Clinical Application Specialist during user training.

You will be contacted:

Bracco will provide further training to all CardioGen-82 users on proper daily quality control measures, especially the testing and documentation for strontium breakthrough. We will be contacting you in the next week to schedule a Quality Review visit to review the mandatory CardioGen-82 Quality Control and appropriate documentation of those procedures. During our Quality Review visit, we will also review Bracco's requirements for total saline volume when using the CardioGen-82 generator.

As with the use of any radioactive material, care should be taken to minimize radiation exposure to the patient, consistent with proper patient management, and to ensure minimum radiation exposure to occupational workers. This goal can readily be accomplished by following the FDA approved instructions briefly mentioned above and set forth in full in the attached sections of the product label. It is therefore important that you ensure that your patients do not inadvertently receive, and your technologists are not inadvertently exposed to, Sr-82 or Sr-85 in quantities beyond the labeled specification limits.

Please call the Bracco Professional Services department at (800) 257-5181, or contact your Bracco Clinical Applications Specialist, if you wish to discuss this further or have any questions or comments.

Sincerely,

BRACCO DIAGNOSTICS INC.

A handwritten signature in black ink that reads "Alberto Spinazzi". The signature is written in a cursive, flowing style.

Alberto Spinazzi, M.D.
Senior Vice President
Global Medical & Regulatory Affairs
Bracco Diagnostics Inc.
107 College Road East
Princeton, NJ 08540

CardioGen-82[®] Quality Control Procedures (Perform Daily)

(Rubidium Rb 82 Generator)

QC Preparation:

- Aseptic techniques should be employed throughout each procedure
- Waterproof gloves are to be worn
- Allow 10 minutes between elutions
- **Elute only with additive free 0.9% sodium chloride injection USP**
- Survey the waste bottle and empty the contents daily according to department radiation safety regulations
- **The waste bottle should be emptied every morning prior to system use or at the end of the day.**
- Infusion System Control Panel Settings for Quality Control:

Mode Switch:	Automatic Infusion
Elution Volume:	99 ml
Patient Volume:	50 ml
Patient Dose:	will vary depending on QC test
Dose Rate:	1 mCi/sec
Flow Rate:	50 ml/min

1st Elution: The Generator Column Wash

1. Place new elution vial in lead container
2. Attach 20 gauge needle to patient administration set and insert into the elution test vial.
3. Insert vent needle into the elution test vial (make sure the vent needle does not extend below the 50 ml fill point)
4. **Set the patient dose to 99 mCi**
5. **Set the patient volume to 50 ml**
6. Confirm the infusion mode is set to automatic infusion
7. Confirm the syringe pump is properly filled
8. Start infusion (observe ALARA principles)
9. Allow for adequate decay, survey and discard the elute and vial according to department radiation safety regulations

**DO NOT INFUSE
THE 1st ELUTION
INTO PATIENTS.**

The information on this page was taken from the CardioGen-82 prescribing information as well as the Infusion System User's Guide.

CardioGen-82[®] Quality Control Procedures

(Rubidium Rb 82 Generator)

2nd Elution: Sr-82 and Sr-85 Breakthrough Test

1. Allow **10 minutes** after the previous elution for generator regeneration
2. Place new elution vial in lead container
3. Attach 20 gauge needle to patient administration set and insert into the elution test vial
4. Insert vent needle into the elution test vial (make sure the vent needle does not extend below the 50 ml fill point)
5. **Set the patient dose to 99 mCi**
6. **Set the patient volume to 50 ml**
7. Confirm the infusion mode is set to automatic infusion
8. Confirm the syringe pump is properly filled
9. Collect and assay a 50 ml sample of Rb-82:
 - Start infusion (observe ALARA principles)
 - When the Inject Start/Stop light goes out, start the provided timer
 - *See decay factor table from the QC log sheets for additional assay times
 - Take the shielded elution test vial to the dose calibrator for assay
 - Assay the eluate in the elution test vial at 2 minutes and 30* seconds or 3 minutes and 45 seconds per Bracco direction, record the dose calibrator reading (Note: keep the timer running)
 - *See decay factor table from the QC log sheets for additional assay times
 - Correct the dose assay for decay
 - Set shielded elution test vial aside to measure for breakthrough at 60 minutes post end of elution (EOE).
10. Sr-82 and Sr-85 Breakthrough Assay:
 - Assay the elute in the elution test vial at 60 minutes post EOE, record the dose calibrator reading
 - Calculate the amount of Sr-82 breakthrough according to the Breakthrough Worksheet
 - Sr-82 content must not exceed 0.02 uCi/mCi of Rb-82
 - Calculate the amount of Sr-85 breakthrough according to the Breakthrough Worksheet
 - Sr-85 content must not exceed 0.2 uCi/mCi of Rb-82
 - If breakthrough is detected above the allowable limits, do not use the generator and contact Bracco Diagnostics, Inc.

**DO NOT INFUSE
THE 2nd ELUTION
INTO PATIENTS.**

If the results from Strontium Sr-82/Sr-85 break through testing exceed one-tenth (1/10) of the specification limit (1/10 of the specification limit = 0.002 µCi Sr-82/mCi Rb-82 or 0.02 µCi Sr-85/mCi Rb-82), then Bracco Diagnostics Inc. recommends performing the Rb-82 assay and the Sr-82/Sr-85 breakthrough testing at least twice daily (i.e., beginning and middle of day). This additional test should be initiated on the day the Sr82-/Sr-85 levels exceed 1/10 of the specification limit indicated above and each day thereafter.

11. Retain the Breakthrough Worksheet according to department record retention policies

The information on this page was taken from the CardioGen-82 prescribing information as well as the Infusion System User's Guide.

CardioGen-82[®] Quality Control Procedures

(Rubidium Rb 82 Generator)

3rd Elution: Infusion System Calibration

1. Allow 10 minutes after the 2nd elution for generator regeneration
2. Place new elution vial in lead container
3. Attach 20 gauge needle to patient administration set and insert into the elution test vial.
4. Insert vent needle into the elution test vial (make sure the vent needle does not extend below the 50 ml fill point)
5. Set the patient dose limit to the typical patient dose used (10-60 mCi)
6. Set the patient volume limit to 50 ml
7. Confirm the infusion mode is set to automatic infusion
8. Confirm the syringe pump is properly filled
9. Calibration Assay:
 - Start infusion (observe ALARA principles)
 - When the Inject Start/Stop light turns off, start the provided timer
 - Take the shielded elution test vial to the dose calibrator just prior to the time of assay
 - Assay the elute in the elution test vial at 2 min and 30* sec or 3 min and 45 sec per Bracco direction, record the dose calibrator reading
 - *See decay factor table from the QC log sheets for additional assay times
 - Calculate the calibration ratio according to the Calibration Worksheet provided
 - Initial calibration of a new generator should be within 0.95 and 1.05
 - Daily calibration should be within 0.90 and 1.10
 - If calibration exceeds limits, calculate a new calibration factor and enter the new calibration number into the infusion system and repeat calibration elution and assay
 - Continue to perform calibrations until the ratio falls within the recommended guidelines on the Calibration Worksheet
 - Retain the Calibration Worksheet according to department record retention policies

**DO NOT INFUSE
THE 3rd ELUTION
INTO PATIENTS.**

The information on this page was taken from the CardioGen-82 prescribing information as well as the Infusion System User's Guide.