The Strontium/Rubidium Generator Incident

Presented to the Nuclear Regulatory Commission's Advisory Committee on Medical Use of Isotopes (September 22-23, 2011)

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Disclaimer Statement

The professional opinions I express today, and the mention or display of any commercial products, is neither an endorsement nor necessarily reflect the official position of the Food and Drug Administration or the Department of Health and Human Services.

Since this is currently an ongoing investigation, the objective of this presentation is simply to provide an informational update to members of this committee during this public meeting.

With me today are:

- Dwaine Rieves, MD, Director
  - Division of Medical Imaging Products (DMIP)
  - Office of New Drugs
  - Center for Drug Evaluation and Research

- Lucie Yang, MD – Team Leader within DMIP
- Ira Krefting, MD- Deputy Director for Safety

Rubidium-82

- Rb-82 is a myocardial infusion agent with an effective dose of 3- 4 mSv (0.3 – 0.4 rem).
- It is a positron emitter*, emitting two 511 keV annihilation photons and a 776 keV gamma.
- It is produced using a Sr/Rb generator with a 28 day generator life.
- Sr-82 decays (T ½ = 25.5 days) to Rb-82.
- Sr-85 is also present and emits a 514 keV gamma (T ½ = 64.8 days).

*Imaged using positron emission tomography (PET)

Customs and Border Protection* (Department of Homeland Security)

- This past year CBP detected unexpected levels of Strontium -82 and Strontium - 85 in two patients, at two different US entry sites, as they reentered the United States.

- These two patients had been scanned two and four months earlier, in two different states, at two different clinical sites with Cardiogen®, a cardiac imaging agent, which uses Rb-82 as the imaging agent.

Customs and Border Protection* (Department of Homeland Security)

By identifying the spectra, Sr-82 and Sr-85 were positively identified and was reported to FDA.

Breakthrough limits are 0.02 µCi/mCi for Sr-82; and 0.2 µCi/mCi for Sr-85

* Myers SC and Felsher PD: Potential Sr-82/Sr-85 Breakthrough in Rb-82 Generators. LA-UR-11-04016, Los Alamos National Laboratory.

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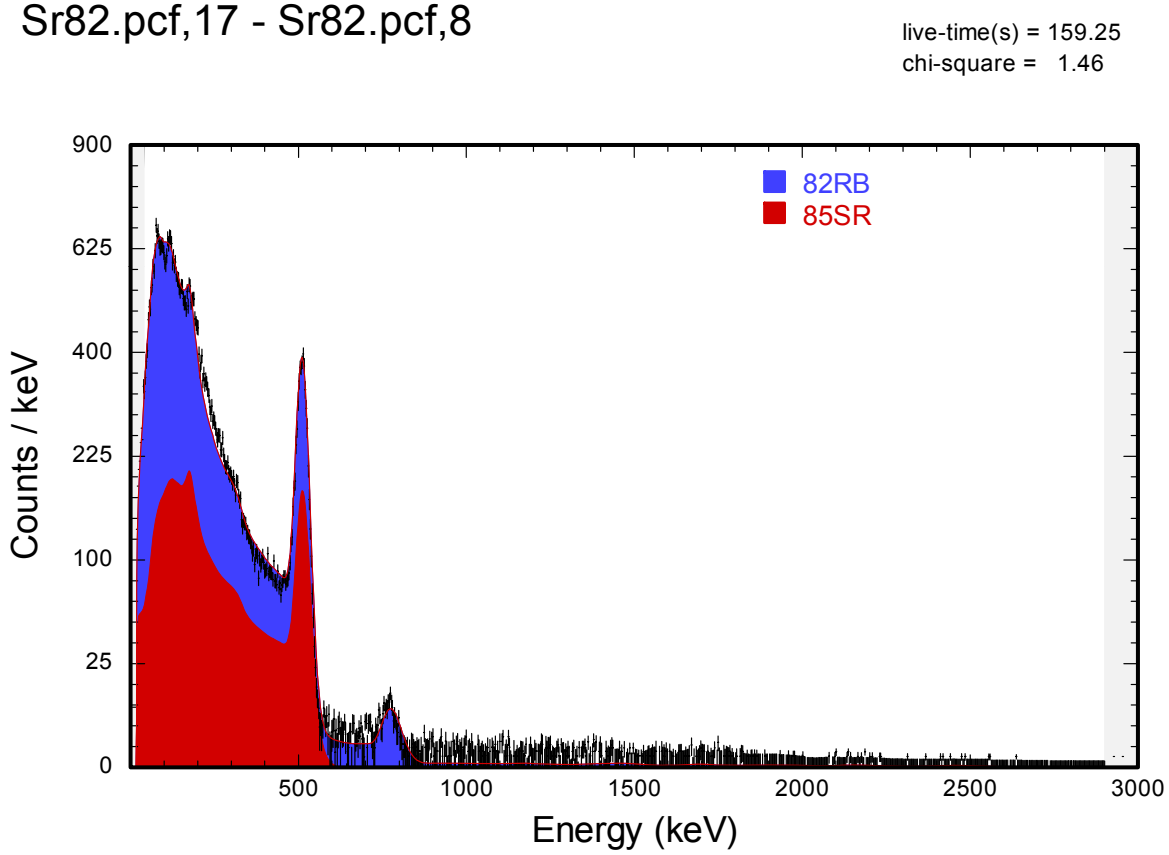

On July 15th, 2011 FDA issued a drug safety communication

FDA expressed concerns for “the potential for inadvertent, increased radiation exposure”

2011http://www.fda.gov/Drugs/DrugSafety/ucm263112.htm

Contamination and Radiation Dose

- Preliminary estimates suggested serious breakthrough of the contaminants Sr-85 and Sr-82, independently verified to be much greater than the permissible limits.

- FDA stated “that the risk of harm from this exposure is minimal.”, but ...”the excess radiation the two patients received is similar to that other patients may receive with cumulative exposure to certain other types of heart scans…”.

Contamination and Radiation Dose

For the two patients, preliminary estimates were as high as 90 mSv (9 rem), later recalculated to less than 50 mSv (5 rem.)*

*Organ dose estimates have an inherent level of uncertainty due to assumptions, different mathematical models, patient dimensions, and individual pharmacokinetics (organ uptake and clearance).

Lack of information

FDA did not know the number of patients using Cardio-Gen-82 generators.

We also did not know the cause of the breakthrough….

Lack of information

"At this time, it is unknown whether this safety issue is due to a product problem involving generator failure or due to user error, or a combination of both factors. FDA is actively investigating the root cause of this issue and will take appropriate regulatory actions as warranted. FDA will promptly notify the public when a conclusion is made."

"Multiple assumptions are involved in estimating the extent of this radiation exposure… including discussion with the NRC."

Bracco Diagnostics, Inc, recalls Rubidium generator

- In a July 26, 2011 Drug Safety Communication, FDA reported that the manufacturer had voluntarily recalled Cardio-Gen-82.
- http://www.fda.gov/Drugs/DrugSafety/ucm265278.htm
- "FDA has determined that the current CardioGen-82 manufacturing procedures are not sufficient to ensure reliable performance of the generator used to produce the Rb-82 chloride injection."

Summary

- At this time the investigation is ongoing.
- Bracco Diagnostics, Inc., agreement states, and other federal agencies are currently involved with this investigation.
- As the deadline for printing this presentation was prior to the meeting date, and this is an ongoing investigation, we hope some additional information can be presented at the meeting.

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Acronyms

- CBP – Customs and Border Protection
- DHHS – Department of Health and Human Services
- FDA – Food and Drug Administration
- NRC – United States Nuclear Regulatory Commission
- Rb – Rubidium
- Sr – Strontium