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FDA Update: The Strontium/Rubidium Generator

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Committee on Medical Use of Isotopes
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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 still ongoing, the objective of this presentation is simply to provide an informational update to members of this committee during this public meeting.





Review

- Two nuclear medicine patients were detected at two independent border crossings by DHS* (Summer, 2011).
- DoE*'s LANL* positively identified nuclides as Sr-85 and Sr-82, referred to FDA. Subsequently verified at ORNL* (Aug, 2011).
- Patients had been scanned 66 and 106 days earlier with Cardiogen® (Rb-82, a positron emitter, $T_{1/2} = 75$ seconds) at two independent clinical sites in Nevada and Florida.
- Bracco voluntarily recalled product in July, reintroduced in February, 2012, with new label.
 - DHS- Dept of Homeland Security
 - DoE- Dept of Energy
 - LANL Los Alamos National Laboratory
 - ORNL- Oak Ridge National Laboratory



How widespread?

- Several hundred patients have been screened with survey meters, and high activity patients underwent whole body counting (WBC) at ORNL or LLNL*.
- SR-85 detected at several additional sites, but these were at or below breakthrough levels. We did not observe serious levels at other than the two index sites.
- Vast majority of contaminated patients limited to the two index sites which were also the highest volume sites.
- After WBC three (3) patients from one site exceeded the 50 mSv Medical Event criteria.

*LLNL- Lawrence Livermore National Laboratory



Challenges

- Technical- Generator issues, detection of Sr-82 and Sr-85 in patients, accuracy of dose calibrator and infusion systems.
- Logistical- Patients counted many months after scans, coordination with Bracco and other agencies.
- Regulatory- Different statutes, different responsibilities, different jurisdictions.



Radiation doses higher than necessary, but “unsafe?”

• Rb-82	1.2 mSv*
• Rb-82 + Sr breakthrough	1.2 < 50 mSv -> ?
• Tc-99m**	~10 – 13 mSv
• Tl-201**	41 mSv
• Fl Coronary angiography**	~7 mSv
• CT coronary angiography**	~16 mSv
• Annual Occupational limit**	50 mSv

* Whole body dose (Original Cardiogen® Label)

**Dose estimates from: Effective doses in Radiology and Nuclear Medicine
Radiology: Volume 248; No 1- July 2008



FDA considered this both a drug purity and an end user issue

- Breakthrough amounts of Sr-85 and Sr-82, considered to be impurities, should have been limited to 15 μCi (Sr-85) and 1.5 μCi (Sr-82) for 75 mCi of Rb activity.
- One index patient had amounts **7 and 125 times** these limits, 105 μCi of Sr-85 and 188 μCi of Sr-82, but these estimates had a high degree of uncertainty associated with them.
- This yielded an effective dose of about 49 mSv, based on assumptions and which dose coefficients were used, or **about 40 x's the prescribed label dose of 1.2 mSv.**

Rubidium-82 Dose Estimates Vary (3 different dose coefficients)

- **“Rb-82 is a myocardial infusion agent with an effective dose of 3- 4 mSv (0.3 – 0.4 rem).” ***
 - 1.2 mSv (0.12 rem) whole body dose
(1989 Bracco Label) for 75 mCi administered activity.
 - 4.8 mSv (0.48 rem) effective dose (E)
(ICRP 60 dose coefficients for 75 mCi activity)
 - 1.3 mSv (0.13 rem) (whole body); 3.5mSv (E)**
(New Label = Senthamizhchelvan S et. al. Human biodistribution and radiation dosimetry of 82Rb. J Nucl Med, 2010; 51:1592-9) for 75 mCi of Rb activity)

***From September ACMUI meeting**

**** effective dose (ICRP 60)**



Dose from breakthrough limits?

(How much additional radiation from strontium breakthrough?)

	Whole Body Dose (Original Bracco PI)	Effective Dose	Kidney (Organ with highest Rb dose)	Bone Marrow (Organ with highest Sr dose)
Rb-82	1.2 mSv	4.8 mSv	24 mSv	1.1 mSv
Sr-82	0.2 mSv	0.3 mSv	0.1 mSv	1.3 mSv
Sr-85	0.5 mSv	0.4 mSv	0.3 mSv	0.9 mSv
Total (% due to breakthrough))	1.9 mSv 58%	5.5 mSv 15%	24.4 mSv 2%	3.3 mSv 200%



Generator testing showed volume was critical factor

- Cumulative volume was more accurate predictor of breakthrough than time.
- Expiration time limit changed from 28 days to 42 days, volume limit added to label.
- New label reflects these changes.



Major Label Changes (1) (FDA Black Box Warning)

Expiration of generator

- **Increased from 28 to 42 days,**
- **When 17 liters of total volume is eluted (at 14 liters additional breakthrough testing required).**
- **When new, 50% lower, breakthrough limits reached:**
 - Sr-82 (0.02 μCi to **0.01 μCi per mCi of Rb-82)**
 - Sr-85 (0.2 μCi to **0.1 μCi per mCi of Rb-82)**



Major Label Changes (2) Breakthrough testing

When **new Alert Limits reached**, breakthrough testing must be performed twice daily. These are 1 fifth the level of the new breakthrough limits:

For Sr-82 0.002 μCi per mCi administered Rb-82

For Sr-85 0.02 μCi per mCi administered Rb-82



Why did FDA allow product back on the market?

- FDA considers new label restrictions sufficient to ensure the product is safe, if used properly, although FDA still has concerns about end user issues beyond its jurisdiction.
- We currently question the accuracy of dose calibration/infusion system for Rb administration and strontium detection.
- We are closely monitoring the product reintroduction.



Are new, lower Alert limits detectable?

For Sr-82, $(0.002 \mu\text{Ci per mCi administered Rb-82}) \times (\text{minimum } 30 \text{ mCi administered Rb-82}) =$
0.06 μCi , which is minimum activity, in as much
as 100 ml of solution. Since volume used in
detectors may vary, as well as counting time and
background, these factors will affect the minimum
detectable activity.



Rb-82, Sr-82, and Sr-85 are detected indirectly, spectra not detected.

- Label instructions are 23 years old, using old technology.
- Rely on manufacturer's Sr-85/Sr-82 ratio.
- After 1 hour decay, all of Rb-82 has decayed away, and any new activity detected is assumed to be to Rb-82, in secular equilibrium with Sr-82 from breakthrough. Sr-82 is estimated based on measured activity.
- Sr-85 is then derived from the Sr-85/Sr-82 ratio.



Many stakeholders aware of these concerns regarding accuracy, and detectability of the dose calibrator and infusion system

- Federal and state regulatory authorities
- Industry, Manufacturers, Vendors
- Clinical Sites with professional staff



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Questions?



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