UNITED STATES
NUCLEAR REGULATORY COMMISSION
OFFICE OF NUCLEAR MATERIALS SAFETY AND SAFEGUARDS
WASHINGTON, D.C. 20555-0001

January 12, 2016

NRC INFORMATION NOTICE 2016-03: REVISION TO THE NATIONAL INSTITUTE OF STANDARDS AND TECHNOLOGY STANDARD FOR RADIUM-223 AND IMPACT ON DOSE CALIBRATION FOR THE MEDICAL USE OF RADIUM-223 DICHLORIDE

ADDRESSEES

All U.S. Nuclear Regulatory Commission (NRC) medical licensees, NRC Master Materials Licensees, Agreement State Radiation Control Program Directors, and State Liaison Officers.

PURPOSE

The NRC is issuing this Information Notice (IN) to alert addressees that the National Institute of Standards and Technology (NIST) revised its primary standard for radium-223 (Ra-223) and to convey the impact this revision will have on the calibration of patient doses of Ra-223 dichloride (trade name Xofigo®). Recipients should review the information contained in this notice for applicability to their facilities and consider taking appropriate action, if necessary. However, the information conveyed in this notice is not a new NRC requirement; therefore, no specific action or written response to this notice is required.

The NRC is providing this notice to the Agreement States for information and distribution to medical use licensees, as appropriate.

BACKGROUND

Ra-223 dichloride is an injectable radiopharmaceutical used to treat skeletal metastases in advanced, castration-resistant prostate cancer. Ra-223 emits alpha particles and has a half-life of 11.4 days. Once in the body, Ra-223 dichloride mimics calcium and forms complexes in areas of increased bone turnover, such as sites of bone metastases. Ra-223 dichloride kills tumor cells through highly localized, short-range alpha irradiation. Although Ra-223 is primarily an alpha-emitter, the activity of Ra-223 can be measured in a radioisotope dose calibrator that has been calibrated with NIST-traceable Ra-223 reference material.

ML15264B095

Following U.S. Food and Drug Administration approval in May 2013, Bayer Pharma AG (Bayer), began commercial distribution of Xofigo® domestically. Bayer provided Xofigo® customers with a NIST-traceable Ra-223 standard syringe and an appropriate dial setting for dose calibrators based on NIST data published in 2010.[1]

DESCRIPTION OF CIRCUMSTANCES

In 2013, NIST was made aware of studies performed by the National Physical Laboratory (NPL) (the National Measurement Institute of the United Kingdom) in which an approximately 10 percent difference was found between NPL's activities obtained using several primary methods and those obtained with the calibration factors published by NIST from 2010. Subsequently, NIST performed additional testing using more robust methods than previously available to verify NPL's results and confirmed that activity readings were lower than expected. On March 11, 2015, NIST published information[2] regarding the revised primary standard for Ra-223 resulting in a numerical increase of 10.5 percent for the new primary standard. This change was only to the numerical value of the quantity of Ra-223, as the actual amount of Ra-223 in the primary standard did not change.

Bayer notified Xofigo® customers of the NIST standardization change and future labeling and calibration impacts in a letter dated March 18, 2015. See "Bayer Letter to Healthcare Professionals for Ra-223 NIST Standardization Issue," available in ADAMS under Accession No. ML15264B158. In the letter, Bayer stated that they will provide customers with a new NIST-traceable Ra-223 standard syringe and dose calibration dial setting based on the NIST revised primary standard. Bayer also stated that they will increase the numerical values listed on the package label by approximately 10 percent. For example, the labeling of the patient dosage will be updated from 50kBq/kg of body weight to 55kBq/kg of body weight. Additionally, Bayer stated that the manufacturing and product documentation will be updated and labeled as 1100 kBq/mL (previously 1000 kBq/mL) and 6.6 MBq/vial (previously 6.0 MBq/vial).

The NRC's licensees are typically authorized for the possession and medical use of Ra-223 dichloride in the millicurie range. Xofigo® doses are administered in the ***micro***curie range, so the NRC does not anticipate the need to update licenses as a result of the new primary NIST standard. Furthermore, Bayer stated in its March 18, 2015, letter that the revised NIST standard for Ra-223 does not change the actual amount of Ra-223 dichloride being administered to patients and will not impact the safety and efficacy of Xofigo®.

---

[1] J. T. Cessna and B. E. Zimmerman, Standardization of radium-223 by liquid scintillation counting, Appl. Radiat. Isot. **68**, 1523-1528 (2010) and D. E. Bergeron, B. E. Zimmerman, and J. T. Cessna, Development of secondary standards for 223Ra, Appl. Radiat. Isot. **68**, 1367-1370 (2010).

[2] B. E. Zimmerman, D. E. Bergeron, J. T. Cessna, R. Fitzgerald, and L. Pibida, Revision of the NIST Standard for 223Ra: New Measurements and Review of 2008 Data, Journal of Research of NIST, **120**, 37-57 (2015).

As stated in the purpose section of this IN, this notice does not convey any new NRC requirements. Therefore, licensees are not required to take any action based on this notice. As stated in its March 18, 2015 letter, Bayer is contacting healthcare providers to provide information on how to obtain an updated NIST-traceable standard and to prepare for future changes in the dose calibrator dial setting. The new dial setting should not be used for verifying the activity in patient dosages until Bayer implements label changes in 2016. Bayer will notify Xofigo® customers of the label change via letter a few weeks before the implementation date. When the label change occurs and the new dial setting is to be implemented, licensees may update internal procedures, as needed (e.g., to reflect the new dial setting on the dose calibrator).

CONCLUSION

Bayer's March 18, 2015, letter emphasizes that no immediate action on the part of its customers is necessary for meeting the new calibration standard. NRC advises affected licensees to continue to use the existing NIST-traceable Ra-223 standard syringe and calibration dial setting until notified otherwise by Bayer.

CONTACT

This notice requires no specific action or written response. Licensees may contact Bayer at (888) 842-2937 or visit www.xofigo.us.com for additional information on how to obtain an updated NIST-traceable Ra-223 standard syringe and to prepare for future changes in the dose calibrator dial setting. For regulatory questions, please contact the technical contact below.

/RA Pamela Henderson for/

Daniel S. Collins, Director
Division of Material Safety, State, Tribal
and Rulemaking Programs
Office of Nuclear Material Safety
and Safeguards

Technical Contact: Michael Fuller, NMSS
Phone: (301) 415-0520
Email: Michael.Fuller@nrc.gov

Note: NRC generic communications may be found on the NRC public Web site, http://www.nrc.gov, under “NRC Library” > “Document Collections

As stated in the purpose section of this IN, this notice does not convey any new NRC requirements. Therefore, licensees are not required to take any action based on this notice. As stated in their March 18, 2015 letter, Bayer is contacting healthcare providers to provide information on how to obtain an updated NIST-traceable standard and to prepare for future changes in the dose calibrator dial setting. The new dial setting should not be used for verifying the activity in patient dosages until Bayer implements label changes in 2016. Bayer will notify Xofigo® customers via letter a few weeks before the implementation date of the label change. When the label change occurs and the new dial setting is to be implemented, licensees may update internal procedures, as needed (e.g. to reflect the new dial setting on the dose calibrator).

CONCLUSION

Bayer's March 18, 2015, letter emphasizes that no immediate action on the part of its customers is necessary for meeting the new calibration standard. NRC advises affected licensees to continue to use the existing NIST-traceable Ra-223 standard syringe and calibration dial setting until notified otherwise by Bayer.

CONTACT

This notice requires no specific action or written response. Licensees may contact Bayer at (888) 842-2937 or visit www.xofigo.us.com for additional information on how to obtain an updated NIST-traceable Ra-223 standard syringe and to prepare for future changes in the dose calibrator dial setting. For regulatory questions, please contact the technical contact below.

/RA Pamela Henderson for/

Daniel S. Collins, Director
Division of Material Safety, State, Tribal
and Rulemaking Programs
Office of Nuclear Material Safety
and Safeguards

Technical Contact: Michael Fuller, NMSS
Phone: (301) 415-0520
Email: Michael.Fuller@nrc.gov

Note: NRC generic communications may be found on the NRC public Web site, http://www.nrc.gov, under “NRC Library” > “Document Collections

ADAMS Accession No. ML15264B095 *via email

OFFICE	MSTR/MSEB	MSTR/MSEB	MSTR/MSEB	OGC	MSTR
NAME	*ACockerham	AMcIntosh	DBollock	*NLO	PHenderson for DCollins
DATE	9/25/15	10/14/15	10/1/15	1/7/16	1/12/16

OFFICIAL RECORD DOCUMENT