

Date: March 31, 2016
To: Medical Licensees
From: Radioactive Materials Unit
Subject: 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

Informational Notice 2016-01

The Minnesota Department of Health (MDH) is issuing this Information Notice (IN) to alert medical licensees 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®). Licensees should review the information contained in their notice for the applicability to their facilities and consider taking appropriate action, if necessary.

The information in this notice is not a new Minnesota Department of Health (MDH) requirement and no specific action or response to this notice is required.

Summary of the Issue:

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.

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

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 information² 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. In the letter, Bayer stated that they will provide customers with a new NIST-traceable Ra-223 standard syringe and dose calibrator dial setting based on the NIST revised primary standard. Bayer also stated that they would 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 50 kBq/kg of body weight to 55 kBq/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).

MDH'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 *microcurie* range, so MDH does not anticipate the need to update licenses because 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[®].

Recommended Action:

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. MDH advises affected licensees to continue to use the existing NIST-traceable Ra-223 standard syringe and calibration dial setting until notified otherwise by Bayer.

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).