Applied Radiation and Isotopes 68 (2010) 1367–1370

Contents lists available at ScienceDirect

Applied Radiation and Isotopes

journal homepage: www.elsevier.com/locate/apradiso

Development of secondary standards for ^{223}Ra

Denis E. Bergeron *, Brian E. Zimmerman, Jeffrey T. Cessna

Physics Laboratory, National Institute of Standards and Technology, 100 Bureau Drive, Stop 8462, Gaithersburg, MD 20899, USA

ARTICLE INFO

Keywords:
Dose calibrator
Secondary standardization
Ionization chamber
^{223}Ra

ABSTRACT

Ra-223 is a bone-seeking alpha emitter currently being evaluated as a radiopharmaceutical. Concurrent with the primary standardization, NIST established that calibration factors currently used for radionuclide calibrators in the clinical setting give readings 5.7–8.7% higher than the NIST calibrated activity. This work describes the determination of calibration factors specific to dose vials and syringes. Using the calibration factors derived with standard ampoules to measure syringe activities can give readings up to 3.6% too high.

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1. Introduction

The National Institute of Standards and Technology (NIST) recently developed a radioactivity measurement standard for a ^{223}Ra solution. A calibration factor for the NIST "4π"γ ionization chamber (IC) (Calhoun, 1987) was established based on activity measurements (Cessna and Zimmerman, 2009) via the CIEMAT/NIST ^{3}H-standard efficiency tracing method (Coursey et al., 1986; Zimmerman and Collé, 1997) of liquid scintillation (LS) counting. Radium-223 is being evaluated as a radiopharmaceutical for the treatment of skeletal metastases. As an alkaline earth metal, Ra exhibits intrinsic bone-seeking behavior, so that ligation (immunoconjugation or, for example, phosphonation) is not required for efficient, targeted delivery. Furthermore, while most commercial formulations currently available for this treatment are β-emitters, ^{223}Ra decays in a chain that results in the emission of a total of four alphas and two betas per decay of the parent. Alpha emitters are considered attractive for the treatment of metastases due to intrinsically high linear energy transfer and short path length; thus, high specificity and high efficacy are predicted. In particular, the rapid emission of α-particles from the first three nuclides in the ^{223}Ra decay chain has been touted as ensuring strong, targeted cytotoxicity (Brechbiel, 2007; Howell et al., 1997; Imam, 2001; Macklis et al., 1988; McDevitt et al., 1998; Vaidyanathan and Zalutsky, 1996).

In order to conduct clinical trials in the United States, high standards of accuracy in activity measurements must be met. In clinical applications, activity measurements are most often achieved with commercially available radionuclide calibrators which incorporate a reentrant IC, and are commonly referred to as "dose calibrators". To achieve acceptable levels of accuracy, appropriate calibration factors, or "dial settings" (DS), must be employed. Currently, no manufacturer recommended settings exist for ^{223}Ra. In our recent standardization, we found that the DS's adopted in previous trials gave average readings 5.7%–8.7% higher than the NIST calibrated activity. These measurements were performed in the 5 mL NIST ampoule geometry, which is the standard geometry for all DS's published by Capintec for their radionuclide calibrators.[1]

Because the characteristics (wall thickness, chemical composition, etc.) of the sample affect attenuation, accurate measurements require geometry-specific DS's (Calhoun et al., 1987; Zimmerman and Cessna, 2000; Zimmerman et al., 2001). Given the relatively low energy photons (<150 keV) and bremsstrahlung characteristic of the ^{223}Ra decay, attenuation effects might be expected to be relatively large. As part of the Nuclear Medicine Standards Program at NIST, we report here empirically determined DS's for several clinically relevant source geometries (dose vials and syringes) for a set of representative commercial radionuclide calibrators.[2]

2. Materials and methods

A total of four experiments, each using a separate shipment of ^{223}Ra solution, were performed. The solutions that were shipped to NIST were designated by Algeta, ASA (Oslo, Norway) as the

[1] Certain commercial equipment, instruments, or materials are identified in this paper to foster understanding. Such identification does not imply recommendation by the National Institute of Standards and Technology, nor does it imply that the materials or equipment identified are necessarily the best available for the purpose.

[2] CRC-12, S/N: 12561 (electrometer and chamber); CRC 15-R, S/N: 155544 (electrometer and chamber); CRC 35-R, S/N: 350267 (electrometer and chamber); AtomLab 100, S/N: 1805001 (electrometer), 1757081 (chamber); Keithley 6514A, S/N: 0732150 (electrometer); Vinten 671, S/N: 3-2 (chamber).

* Corresponding author. Tel.: +1 301 975 2282; fax: +1 301 926 7416.
E-mail address: denis.bergeron@nist.gov (D.E. Bergeron).

0969-8043/$ - see front matter Published by Elsevier Ltd.
doi:10.1016/j.apradiso.2009.11.005

"Drug Substance" in their production process and had nominal activity concentrations of 2.5–3.0 MBq g^{-1} at the time of receipt. The composition of the "Drug Substance" consisted of a ^{223}Ra solution in a proprietary buffer solution. In order to maintain a stable composition throughout the studies, the same carrier/buffer solution was used for all dilutions. Over the course of the experiments, the mean solution density was measured as 1.008 g mL^{-1}, with a 0.10% relative standard deviation of the mean.

In four separate experiments, the received solution was brought to a desired volume of master solution by the addition of buffer. An automatic dispenser was then used to dispense this master solution into a NIST 5 mL ampoule and several dose vials and/or syringes containing a range of volumes. Prior to filling, the bottom of each syringe was sealed with epoxy to prevent spillage. No needles were affixed to the ends of the syringes. In total, 15 20 mL crimp-sealed dose vials (FIOLAX, MGlas AG, Münnerstadt, Germany) containing 0.5, 2, or 6 mL of solution; 12 2 mL syringes (BD Plastipak, Becton Dickinson S.A., S. Agustin del Guadalix, Madrid, Spain, REF 300186) containing 0.5, 1, or 2 mL of solution; 3 5 mL syringes (BD Plastipak, Luer-Lok, BD, Franklin Lakes, NJ, USA, REF 300911) containing 2 mL of solution; and 15 20 mL syringes (BD Plastipak, Luer-Lok, BD Drogheda, Ireland, REF 301189) containing 1, 5, 10, 15, or 20 mL of solution were prepared and measured. Dispensed sources contained 0.8–13.8 MBq at the time of measurement.

The massic activity of each master solution was determined by measuring the appropriate ampoule in the NIST "4π"γ IC, using the previously derived calibration factor relative to the appropriate radium (^{226}Ra) reference sources (RRS). The determined activity for each ampoule had an expanded uncertainty of 1.1%; the largest component was the standard uncertainty on the calibration factor (0.53%), followed by the uncertainty due to the positioning of the RRS (0.1%), the uncertainty due to the measurement repeatability (0.07%), the uncertainty on the ratio between the RRS's (0.027%), and the standard uncertainty on the half-life over the measurement interval (0.003%).

Ampoule, dose vial, and syringe sources were measured in each of the NIST-maintained Capintec (CRC-12, CRC-15R, and CRC-35R) and AtomLab-100 radionuclide calibrators. For each measurement sequence, readings were taken at 10 DS's (230–280 in the Capintec chambers, 16.0–18.0 in the AtomLab-100 chamber). For the dose vials and ampoules, the sources were placed at the bottom of the standard dippers. For the 2 and 5 mL syringes, measurements were made in two configurations: hanging from the syringe holder of the standard dippers and resting at the bottom of the standard dippers. No needles were used in this study. Addition of a needle to the syringe would not affect the configuration in the hanging geometry, and would make it impossible to place the syringes at the bottom of the standard dippers. The 20 mL syringes were too wide to hang from the syringe holder of the standard dippers and too tall to rest at the bottom of the standard dippers and were therefore mounted in the hanging position of a syringe holder customized (with a wider bore "hole" for hanging syringes) for use with a 35 mL syringe in a previous study (Zimmerman and Cessna, 1999).

Since the activity of the sources was known, it was possible to select a DS range for each radionuclide calibrator that included the correct setting. This initial range selection utilized the "dialing-in method" described in Zimmerman and Cessna (2000). The range of 10 DS's selected for each chamber was centered on the correct setting for the ampoule. Subsequent determinations used the "calibration curve method" described in Zimmerman and Cessna (1999, 2000). Activity data were decay corrected to a common reference time assigned for each experiment, and the ratio A_{obs}/A_{NIST} (A_{obs}=observed activity; A_{NIST}=calibrated activity) was plotted against the DS. The curves were fit to $y^{-1}=a+bx$, and the NIST-determined DS was assigned when $A_{obs}/A_{NIST}=1$.

In addition to the determination of DS's for the above radionuclide calibrators, calibration factors in terms of pA MBq^{-1} were determined for the NIST-maintained Vinten 671/Keithley 6517A radionuclide calibrator. Ampoules, dose vials, and syringes were all measured resting at the bottom of the standard dipper. This dipper has a well that accommodates a NIST 5 mL ampoule, but is too narrow for a 20 mL dose vial. Therefore, in some experiments, a piece of paper (cut to fit) was placed at the bottom of the dipper to prevent dose vials from falling over, and both dose vials and ampoules were placed at the center of the dipper on the piece of paper. Placement of ampoules in the well or on the piece of paper made no difference in the derived calibration factors to within the precision of the radionuclide calibrators. Syringes could not be placed in the central well, and so rested at the corner of the dipper.

High purity germanium detector gamma ray spectrometry indicated no radionuclidic impurities. Over the region 40 keV $\leq E \leq$ 2100 keV, the limits of detection expressed as massic photonic emission rates were within 30–300 $\gamma\,s^{-1}\,g^{-1}$.

Table 1
NIST-determined dial settings for the different sample geometries in the NIST-maintained Capintec and AtomLab radionuclide calibrators.

	Dial setting	U (k=2)	Δ (%)
CRC-12			
5 mL ampoule	265	4	0.3
20 mL dose vial—average	261	4	−0.8
2 mL syringe—average	271	5	2.0
5 mL syringe—2.0 mL	273	5	2.5
20 mL syringe—5.0 mL	277	5	3.6
20 mL syringe—10.0 mL	274	4	2.9
20 mL syringe—15.0 mL	273	4	2.2
20 mL syringe—20.0 mL	269	4	1.5
CRC-15R			
5 mL ampoule	264	5	0.2
20 mL dose vial—average	265	4	0.2
2 mL syringe—average	265	5	0.5
5 mL syringe—2.0 mL	268	4	1.4
20 mL syringe—5.0 mL	267	5	1.0
20 mL syringe—10.0 mL	269	4	1.6
20 mL syringe—15.0 mL	266	4	0.6
20 mL syringe—20.0 mL	263	4	$6.9\cdot10^{-2}$
CRC-35R			
5 mL ampoule	267	5	$-1.4\cdot10^{-3}$
20 mL dose vial—average	267	4	$-5.5\cdot10^{-2}$
2 mL syringe—average	267	5	$-6.9\cdot10^{-2}$
5 mL syringe—2.0 mL	269	4	0.65
20 mL syringe—5.0 mL	272	4	1.5
20 mL syringe—10.0 mL	270	4	0.95
20 mL syringe—15.0 mL	268	4	$-8.8\cdot10^{-2}$
20 mL syringe—20.0 mL	264	4	−0.74
Atomlab-100			
5 mL ampoule	16.9	0.2	−0.09
20 mL dose vial—average	16.9	0.2	0.24
2 mL syringe—average	16.9	0.2	−0.20
5 mL syringe—2.0 mL	16.8	0.2	0.80
20 mL syringe—5.0 mL	16.8	0.2	0.69
20 mL syringe—10.0 mL	16.8	0.2	0.39
20 mL syringe—15.0 mL	17.0	0.2	−0.80
20 mL syringe—20.0 mL	17.2	0.2	−1.5

Reliance solely on dial settings determined as optimal for the NIST 5 mL ampoule geometry can result in activity measurements that disagree with the NIST-determined activities by as much as 3.6%. U values are calculated by propagating the expanded uncertainty in the activity through the respective fitting equations. The percent discrepancy arising from measuring each source with the ampoule DS is given as Δ. See text for details.

Table 2
Calibration factors for the Vinten 671/Keithley 6514A radionuclide calibrator.

	Calibration factor ($pA\,MBq^{-1}$)	U (k=2) ($pA\,MBq^{-1}$)	Δ (%)
5 mL ampoule	3.50	0.04	$9.4 \cdot 10^{-4}$
20 mL dose vial—average	3.51	0.06	−0.05
2 mL syringe—average	3.65	0.10	3.4
5 mL syringe—2.0 mL	3.63	0.04	3.6
20 mL syringe—5.0 mL	3.59	0.08	3.4
20 mL syringe—10.0 mL	3.55	0.04	1.3
20 mL syringe—15.0 mL	3.50	0.04	−0.15
20 mL syringe—20.0 mL	3.45	0.04	−1.6

No 0.5 mL samples in 2 mL syringes were measured with the Vinten 671/Keithley 6514A radionuclide calibrator. The percent discrepancy arising from calculating the activity of each source with the ampoule calibration factor is given as Δ.

3. Results and discussion

Uncertainty analyses were performed in accord with NIST policy (ISO, 1995; Taylor and Kuyatt, 1994). The combined standard uncertainty on the DS was determined from the combined standard uncertainty on the activity ($<0.8\%$), the measurement repeatability (standard deviation of DS's derived with different sources of the same geometry, $<0.5\%$), the uncertainty on the half-life ($<5 \cdot 10^{-5}\%$), and the average standard uncertainty on the curve fit ($<0.4\%$). The dominant contribution to the DS uncertainty was always the combined standard uncertainty on the activity. The low activities of the sources with the smallest volumes gave rise to the largest uncertainties, as both the standard deviation of the derived DS's and the average standard uncertainty on the curve fit are larger for sources with lower activity; of these two uncertainty factors, the standard deviation of the derived DS's was consistently dominant. The expanded uncertainty on the measured activity due to the DS uncertainty is in most cases similar to the expanded uncertainty on the activity (1.1%, k=2). Even for the lowest activities measured, the expanded uncertainty on the measured activity due to the DS uncertainty is still below 1.7%.

The NIST-determined calibration factors and their uncertainties are given in Tables 1 and 2. Since 5 mL of solution in the NIST 5 mL ampoule is the standard geometry for manufacturer-recommended DS's from Capintec, Tables 1 and 2 also include the discrepancy resulting from measuring each source with the ampoule calibration factors. The percent discrepancy arising from measuring each source with the ampoule DS is determined and an average of these discrepancies is reported for each specific geometry as Δ. The small Δ reported for measuring the 5 mL ampoule at the DS for the 5 mL ampoule can be attributed primarily to the effect of rounding the recommended DS to the nearest whole number (or 10th for the AtomLab).

The NIST-determined DS's for the ampoule and the dose vial geometries for the Capintec and AtomLab systems agreed to within the expanded uncertainty on the DS's ($\pm 1.5\%$). A 1.5% change in DS gives a 0.5% difference in measured activity in the Capintec chambers. In the AtomLab chambers, a 0.6% change in DS gives a 0.5% difference in measured activity. For the dose vial geometry, DS's determined for volumes from 0.5 to 6 mL agree to within their expanded uncertainties and so only the average DS for dose vials is reported for each chamber.

NIST-determined DS's for the syringe geometries differ from the settings for the NIST 5 mL ampoule by as much as 4.3%. Use of the ampoule DS to measure samples in the syringe geometry yields activity values that disagree with the NIST-determined activities by as much as 3.6%. For the 2 mL syringes, variations in the NIST-determined DS's over the 0.5–2 mL volume range fall within the expanded uncertainty on the DS's. For the 2 and 5 mL syringes, the difference in the activities derived using the optimum DS's in the "hanging" geometry and the "bottom" geometry is less than the expanded uncertainty on the activity (note that since affixing a needle to the end of a syringe would access a height intermediate between the hanging geometry and the bottom geometry, DS's appropriate to measurements made with a needle are necessarily encompassed in the same range). The DS values are typically smaller for the Capintec chambers for the hanging geometry; they are larger for the AtomLab chamber. This indicates better detection efficiency in the bottom geometry than in the hanging geometry.

For the 20 mL syringes, significant variation (up to 2.9%) occurs in the NIST-determined DS's over the 5–20 mL volume range. This is due to the decreased geometric efficiency as the liquid level of the radioactive solution approaches the mouth of the IC.

It should be noted that the results of measurements reported herein should be considered valid only for the specific solution composition and containers described, and for the actual NIST-maintained chambers. Users of the reported dial settings should verify their validity on their own systems.

4. Conclusions

NIST has completed the secondary standardization of a solution of ^{223}Ra having a composition specific to a particular drug product submitted in four shipments by the manufacturer. NIST determined calibration factors for each of five NIST-maintained radionuclide calibrators in several clinically relevant geometries. Samples in syringes produce higher ionization currents than samples with the same activity in ampoules or dose vials; measuring at the NIST-determined DS's for the ampoule (instead of the appropriate syringe settings) gives an activity reading that is up to 3.6% too high. Volume effects were insignificant to within the expanded uncertainty for the 20 mL dose vial and 2 mL syringe geometries, but led to discrepancies from the NIST-determined activities as large as 2.9% over the 5–20 mL volume range in the 20 mL syringe geometry.

Acknowledgments

We thank M. Hammond, L. Pibida, and L. King for performing impurity measurements. A portion of this study was funded by Algeta, ASA.

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Discussion:

Q (Mike Woods): Obviously a very clear explanation, can I just ask you to say a little more about the volume effect? I was wondering about the CRC-15R, 5 ml, the fact that it has turned over and come back down, is that just an uncertainty effect or is there some real effect going on there?

A (Denis Bergeron): Difficult to say, that seems to be the only case where it actually does turn over like that and as you noted it is within the uncertainty bars. So, whether that is a real effect to begin with is tough to say. There is no reason in terms of just geometric efficiency why that would happen. If there is some combination of the geometric effect and the chamber sweet spot that could possibly explain it.