The Thesis Committee for John Patrick Metyko
Certifies that this is the approved version of the following thesis:

Intercomparison of Instrumentation Systems for Verification of ^{125}I Brachytherapy Source Strength for Use in Radioactive Seed Localization Procedures

APPROVED BY
SUPERVISING COMMITTEE:

Supervisor: _____
Sheldon Landsberger

Co-Supervisor: _____
William Erwin

Intercomparison of Instrumentation Systems for Verification of ^{125}I Brachytherapy Source Strength for Use in Radioactive Seed Localization Procedures

by

John Patrick Metyko, B.S.; B.A.

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Abstract

Intercomparison of Instrumentation Systems for Verification of ^{125}I Brachytherapy Source Strength for Use in Radioactive Seed Localization Procedures

John Patrick Metyko, M.S.E.

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Supervisor: Sheldon Landsberger

Co-Supervisor: William Erwin

Two different radiation detection instruments, both commonly found in nuclear medicine clinics, were investigated for potential use in ^{125}I brachytherapy seed source strength verification. The goal of this investigation was to determine if either or both of these instruments could replace the air-communicating well-type ionization chamber (standard source strength verification instrument) when the ^{125}I seed is used for radioactive seed localization procedures instead of brachytherapy. In radioactive seed localization, the ^{125}I seed merely localizes the tissue of interest and does not deliver a therapeutic dose to the patient. The ^{125}I seeds are inserted into nonpalpable lesions, which are then removed for biopsy within 5 days. Dose calculations and patient modeling are not performed. As a result of this, stringent source strength accuracy tolerances are not necessary. The accuracy, precision, and reproducibility of an activity

calibrator and an ionization chamber survey meter were assessed and compared to regulatory requirements.

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INTRODUCTION

The use of sealed source radioactive material for brachytherapy cancer treatments originated over 100 ago years with the pioneering ^{226}Ra research by Pierre and Marie Curie (Schwartz *et al*. 2012). ^{125}Iodine (^{125}I) was first used for interstitial brachytherapy in 1965, and its use has increased over time in both volume and variety of applications. The first American Association of Physicists in Medicine (AAPM) report formalizing relevant brachytherapy quality assurance (QA) procedures and safety guidelines was published in 1984 (Svensson 1984). The procedures have evolved in the various AAPM reports since then, and thus far, all of the rules and procedures recommended have been specific to therapeutic use of these sources. In the late 1990s, a novel use of ^{125}I brachytherapy seeds for the localization of non-palpable breast abnormalities in a procedure called radioactive seed localization (RSL) was first reported (Dauway *et al.* 1999).

The intent of the RSL procedure is not therapeutic, and thus the demands of the physicist are not necessarily the same as for brachytherapy. Most importantly, the dose to the patient is much smaller, and there is no detailed dosimetry calculation and treatment planning. The primary concerns for the physicist are keeping the patient dose as low as reasonably achievable (ALARA) while still maintaining seed activity that is sufficient for the surgeon to be able to find it with a gamma probe. Currently, there are no published recommended procedures for how to verify the vendor source strength calibration of the RSL seeds. Physicists have been left to determine if seeds should be

calibrated according to brachytherapy recommended procedures or nuclear medicine (normally unsealed radioactive material) methods and tolerances. At MD Anderson Cancer Center (MDACC) we adopted ^{125}I seed source strength verification procedures similar to that of brachytherapy. This required the purchase of instrumentation not commonly owned or used by nuclear medicine departments. It would be far easier for clinics starting a new RSL program to use instruments that their staff is already familiar with. This is the approach that the Mayo Clinic in Scottsdale, Arizona took (Pavlicek *et al.* 2006). Both IsoAid (RSL seed vendor) and the National Physical Laboratory (the United Kingdom's National Measurement Institute) also use pressurized well chambers to calibrate brachytherapy seeds (Baker *et al.* 2002; IsoAid 2014). The objective of this thesis is to investigate the use of two common nuclear medicine instruments, the activity calibrator (commonly referred to as dose calibrator or radionuclide calibrator) and the ionization chamber survey meter, for the purpose of source strength verification. A batch set of ^{125}I calibration seeds were calibrated on the system currently in place (air-communicating ionization well chamber, designed for measurement of brachytherapy seeds) and then used to determine the correct calibration setting for the activity calibrator and calibration factor for the ionization chamber survey meter. The instruments will be compared in terms of accuracy, precision, and reproducibility in terms of both time and geometry.

BACKGROUND

I-125 Brachytherapy

Brachytherapy is a cancer treatment whereby a radioactive source is inserted into or next to cancerous tissue. "Brachy" means "short distances", hence the name brachytherapy (IAEA 2005). In many situations where brachytherapy is an applicable treatment modality, traditional external radiation beam therapy could also be used. Brachytherapy has the advantage of a more controlled dose distribution. Since the radioactive source is implanted near, or within, the tumor, it is this tumor that receives the largest dose (Schwarz *et al.* 2012). With an appropriately selected radionuclide and initial radioactivity, dose to healthy tissue can be minimized. This is contrary to external beam therapy where there can be significant dose to the healthy tissue surrounding the tumor due to the x-ray beam path passing through the healthy tissue before and after interacting with the tumor (entrance and exit dose). Some cancers typically treated with brachytherapy include prostate, cervical, breast, lung, esophageal, eye, and head and neck. Brachytherapy is often used in combination with external beam therapy (Khan 1984).

Brachytherapy specifically refers to *sealed* radioactive sources. Therefore, in brachytherapy, the treatment location can be controlled with great precision. Dose rates can vary from 0.4 to 2 Gy hr^{-1} in Low Dose Rate (LDR) brachytherapy to over 12 Gy hr^{-1} in High Dose Rate (HDR) brachytherapy (ICRU 1985). The brachytherapy source placement can be either temporary or permanent. Temporary placements range from

minutes to hours. Permanent implants require radionuclides that decay over a few months' time, after which the source remains in place. The radionuclides typically used for brachytherapy include ^{137}Cs, ^{60}Co, ^{192}Ir, ^{90}Sr/^{90}Y and ^{106}Ru for temporary placement and ^{125}I and ^{103}Pd for permanent placement (IAEA 2005).

^{125}Iodine brachytherapy seeds are small and cylindrical with dimensions of 4.5 to 5 mm in length and less than 1 mm in diameter (Rivard 2004). The external shell is titanium, and the interior consists of either tiny resin spheres or silver wires with the radionuclide absorbed onto them (Kutchur *et al.* 1994). ^{125}Iodine decays by electron capture to an excited state of tellurium-125 (^{125}Te), which immediately stabilizes by emitting a 35.5 keV gamma-ray (Nath *et al.* 1995). Characteristic x-rays between 27-32 keV as well as Auger electrons are also emitted during the ^{125}I electron capture process. At these energies, penetrability is limited (2 mm half-value layer in tissue), and the energy is deposited in a highly localized manner, which reduces dose to healthy tissue surrounding the cancer cells (Barnett *et al.* 2007; Schwarz *et al.* 2012). Due to this low-energy radiation and a relatively short half-life of 59.4 days, ^{125}I is considered an optimal permanent implant brachytherapy source.

^{125}Iodine brachytherapy is commonly used to treat prostate cancer, brain cancer, and cancers of the eye. For brachytherapy to be effective, the cancer must be treated at an earlier stage before it has spread significantly to other organs, as it is not effective against tumors that are larger and not well localized (IAEA 2005). The brachytherapy treatment process begins with tumor volume characterization through clinical examination with the assistance of radiography, computed tomography (CT), positron

emission tomography (PET), ultrasound and magnetic resonance imaging (MRI) (ICRU 1993, ICRU 1997). Once an appropriate model of the tumor volume and surrounding tissue has been generated, radioactive source strength and placement must be determined in order to assure sufficient distribution of dose throughout the treatment area while minimizing dose to healthy tissues. For this process to be successful, the radiation field emitted from the brachytherapy source must be very well characterized so that the administered dose follows the treatment planning accurately (Schwarz *et al.* 2012).

AAPM Report No. 51 specifies interstitial brachytherapy seed dosimetry calculation methods including relevant parameters and acceptable levels of uncertainty (Rivard *et al.* 2004). The general formalism assumes a cylindrical seed and yields the dose rate, $D(r,\theta)$, at a point external to the source with position given in polar coordinates. The estimated total 1σ uncertainty in $D(r,\theta)$ is about 6.7%, 5.7%, and 7.3% at 0.1, 1, and 5 cm, respectively. The other quantities that make up the general formalism include the air kerma strength, S_k in units of cGy cm^2 h^{-1}, the dose rate constant, ^ in units of cm^{-2}, the geometry function, $G(r,\theta)$, the anisotropy function $F(r,\theta)$, and the radial dose function $g(r)$. Of these parameters, the clinical medical physicist only measures the air kerma strength, with a typical total 2σ uncertainty of about 3%. The other quantities and their associated uncertainties are determined from tabulated data (ICWG 1990, Williamson 1991, Nath *et al.* 1995, Rivard *et al.* 2004). Air kerma strength is provided by the vendor and must be verified by the medical physicist. The general formulism in polar coordinates for the two-dimensional dose rate at a point (r,θ) due to a cylindrical source is shown in equation 1. The angle, θ, refers to the angle relative to the longitudinal axis of

the seed. Note that the formalism assumes that the dose distribution is cylindrically symmetric about the longitudinal axis of the seed.

$$D(r,\theta) = S_k \wedge [\, G_L(r,\theta) / G_L(r_0,\theta_0) \,]\, g_L(r)\, F(r,\theta) \qquad (1)$$

where $G(r_0,\theta_0)$ is the geometry factor at a reference point (r_0,θ_0).

I-125 Radioactive Seed Localization

One of the preoperative steps for surgical removal of nonpalpable breast tissue abnormalities for biopsy is localization of the lesion so that the surgeon can find it during the procedure. The current standard method of marking the lesion is wire localization (WL), a procedure in which a fine needle is used to insert a wire (or multiple wires) into the abnormality. The needle is then removed, and a mammogram is performed to verify correct wire placement. During the lesion removal surgery, ultrasound is used to locate the wire, and the surgeon removes the wire and surrounding tissue. A recently developed alternative to WL is a procedure called radioactive seed localization (RSL). In RSL small, low-activity (0.2 mCi (7.4 GBq) nominal activity), ^{125}I brachytherapy seeds, pre-packaged sterile into a sterilized needle, are inserted into the nonpalpable lesion and released from the needle, which is then removed from the breast. During the surgery, a hand-held gamma probe indicates the position of the highest count rate (^{125}I energy window) on the surface of the breast. This is the surgeon's incision point. Each seed and lesion are then located and removed with continued assistance from the gamma probe (Jakub *et al.* 2010).

While WL has proven to be effective, there are several problems associated with the procedure (Gray *et al.* 2004). The optimal incision point for the wire is not concurrent with that of the surgery. Thus, a compromise must be made on the surgeon's incision point. It is also difficult during surgery to find the precise location of the wire's end point. This uncertainty in the wire endpoint location increases the risk of either removing too much or too little tissue. The wire may even be cut accidentally during surgery, leaving part of the wire in the body and making the lesion more difficult to locate.

All of these problems are reduced or eliminated in RSL procedures. With RSL, there is a lower rate of repeat surgical procedures. Subjective patient measures have also shown to be favorable for RSL. The procedure is less painful and more convenient for the patient (Pavlicek *et al*. 2006). WL procedures must be performed on the same day as the surgery, which makes scheduling more difficult for hospital staff. WL is typically performed early in the day, and then the patient must wait until later in the day for the actual surgery with very little timing flexibility. On the other hand, RSL insertion is usually performed the day before the surgery, as there is nothing protruding from the patient's body, making it is safe for the patient to leave the hospital. The RSL insertion can be performed up to 5 days prior to the surgery. Exposure rates at contact with the breast (needle entry point) range from 0.2 to 187 μSv h^{-1} and 0.1 to 28 μSv h^{-1} at 1 m (Dauer *et al*. 2013). The Nuclear Regulatory Commission (NRC) guidelines allow release of patients with ^{125}I implants if the total activity is below 9 mCi (333 Gbq), which

is much larger than that which would be expected with RSL procedures (U.S. NRC 1997).

RSL is not a therapeutic procedure, and patient dose is very small. The maximum dose to residual breast tissue has been calculated to be comparable to that of a two-view mammogram (20-30 mGy) (Pavlicek 2006). Because of this, RSL procedures are less dependent on the accuracy of seed activity than when ^{125}I seeds are used in therapeutic procedures. The source strength is still verified (in terms of apparent activity instead of air kerma strength), but there is no requirement for dose distribution modeling (dosimetry). Nonetheless, some physicists currently verify RSL seed vendor calibration by following procedures comparable to standard therapeutic brachytherapy protocol.

Ionization Chamber

Chambers filled with air or gases are the most commonly employed and earliest form of electrical radiation detectors (Leo 1994). An ionization chamber consists of an outer wall, central anode wire and a fill gas, typically argon or other noble gas, which is ionized by incident radiation and secondary electrons from incident photon-wall interactions to create ion-electron pairs. The chamber wall structurally contains the gas, sometimes under pressurization, and acts as a cathode. A high voltage is supplied across the detector volume creating an electric field between the central anode and the cathode (chamber wall), and this electric field causes the electrons and positive ions to travel towards the anode and cathode, respectively. The electrons, once collected at the anode, produce an electric current, which is analyzed by the circuit of the detector system. The

voltage level, and in turn the strength of the electric field, chamber volume and pressurization determine the ionization characteristics of the chamber (Turner 2009). At lower operating voltages, electron-ion pairs simply recombine, while at high operating voltages, a cascade of secondary ionization events results in large charge pulses for each individual primary ionization event.

Each of the ionization chambers investigated herein is operated in the "ionization region" with operating voltages around between 50-300 V. Ionization events in this region result in pulses that are very small. Thus, they are operated in direct current mode, and charge accumulation is measured with an electrometer. In the ionization region, the electric field is sufficient to prevent recombination, but there are no secondary ionizations or charge multiplication factor. The charge created is then directly proportional to the energy deposited into the chamber during the ionization event. Due to this attribute, chambers operated in the ionization region can be used for counting (scaler) applications, gamma-ray and x-ray exposure measurements, Air Kerma measurements, and photon energy spectroscopy (when operated in pulse mode) (Knoll 2010).

Ionization Well Chamber

The well-type ionization chamber is considered standard instrumentation for calibrating brachytherapy seeds for the purpose of verifying vendor seed calibration, which is an important step in assuring patient dose accuracy. This instrument is recommended by governing bodies, accreditation agencies, and relevant expert groups due to its accuracy and long-term stability (Nath *et al.* 1997; Knoll 2010). As the name

"well chamber" implies, the source is placed into a shielded chamber (like a small well). The internal wall is typically made of a thin aluminum alloy (alternatively graphite or air-equivalent plastic) (Carey *et al.* 2012). The detector volume (between internal and external shielding walls) surrounds the narrow, cylindrical space where the seed is inserted. Within the well chamber, background radiation is extremely low. This detector design is necessary for accurate low activity seed calibration. Ionization well chamber responses are extremely geometry dependent, and as such, the seed is typically placed in a thin plastic holder/dipper that is inserted into the well chamber, thus insuring consistent source geometry. A generic well chamber schematic is shown in Figure 1.

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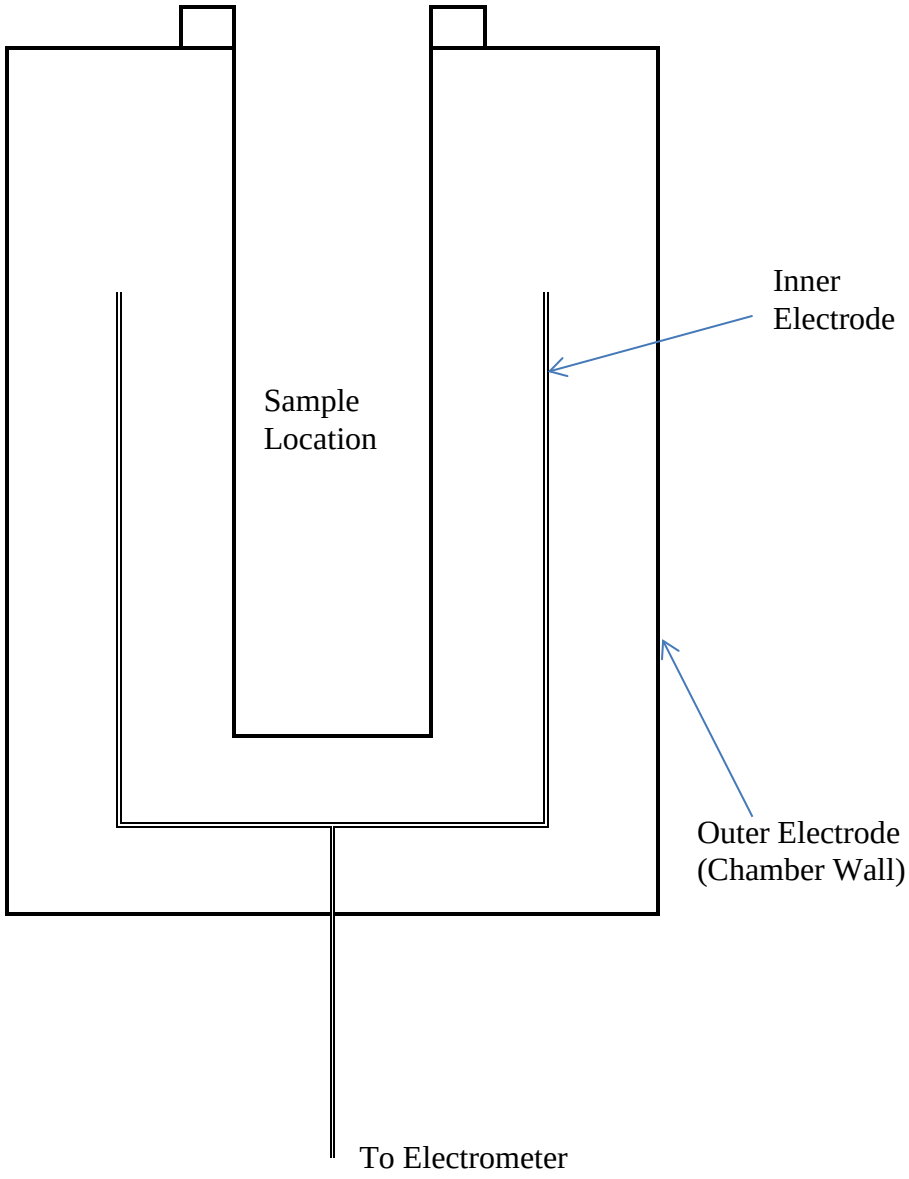

Figure 1. Schematic drawing of a generic well chamber design

Ionization Well Chamber (air-communicating)

Some ionization chamber designs involve a gas (other than air) within the chamber. A high-Z gas (typically a noble gas) is preferred in order to maximize electron interactions and minimize chemical reactivity (Bushberg *et al.* 2002). In designs known as air-communicating well chambers, there is no sealed gas. Instead, a small opening in the chamber wall allows air to flow through the chamber, and it is this air that is ionized. The advantages of utilizing the natural air in the room include improved detector sensitivity to low energy photons (without pressurization the inner shell wall can be thinner which decreases photon attenuation), and there is no risk of response instability from pressurized gas leaking over time (IAEA 2002). A downside of this design is the need to check pressure and temperature before seed calibration and correct the readings according to the variations in atmospheric conditions.

The air-communicating well chamber detection system consists of a thermometer, a barometer, the well chamber itself, and an electrometer. The thermometer and barometer are used to measure atmosphere conditions in the room during the seed assay. When using an air-communicating well chamber, the final results of the assay need to be adjusted to account for differences in atmospheric pressure relative to that of the Accredited Dosimetry Calibration Laboratory (ADCL) room in which the well chamber was calibrated. The current created in the circuit of the ionization chamber is measured by an electrometer, which is a device that indirectly measures current by measuring the change in potential difference in a circuit without actually drawing any current from the circuit (Knoll 2010). This is particularly important for measurements of ionizing

radiation, which involve charge collection on the order of picocoulombs (pC). The electrometer also supplies the voltage needed to create an electric field across the ionization chamber volume. Ideally, current leakage would be zero, but in practice, there is a tiny (femptoampere) amount of leakage. Current leakage must be characterized during calibration and accounted for during use (Kutcher et al. 1994).

The electrometer measurement is displayed in units of charge (pC), which can then be converted to current (pA) by dividing the pC reading by the time passed during measurement (Δt). The electrometer reading is then multiplied by the well chamber calibration coefficient, which is given in units of mCi pA^{-1}. (The calibration coefficient, C, is actually given in units Air Kerma Strength (U)/pA and then multiplied by a conversion factor, where 1 U = 1 uGy m^2 hr^{-1}, and 1 mCi (37 GBq) (apparent activity) = 1.27 U for ^{125}I (Williamson *et al.* 1991). The apparent activity, A_{app}, is "the activity of a hypothetical unfiltered point source of the same radionuclide that would give the same air kerma rate in air at a reference distance (typically 1 m) along the perpendicular bisector of the source." (IAEA 2005). This final result is then corrected for atmospheric conditions (temperature and pressure variation) and current leakage.

$$pC/\Delta t \times Cal\ C \times 1\ mCi/(1.27U) \times N_e \times K_{tp} = \text{Apparent Activity mCi} \quad (2)$$

Where N_e is the electrometer correction factor and K_{tp} is the correction for non-standard temperature and pressure (22ºC and 760 mm Hg, respectively).

The radioactive source is not always characterized in units of apparent activity. For characterization of therapeutic brachytherapy seeds, Air Kerma Strength is the preferred unit, and the step converting U to mCi is removed from equation 2 (Nath *et al.* 1995). ^{125}Iodine seed vendor calibration certificates typically include both units.

Activity Calibrator

The activity calibrator, commonly referred to as “dose calibrator”, is a type of well ionization chamber designed specifically for assaying radioactive materials used in nuclear medicine for imaging or therapy. It has the same cylindrical shape consisting of a heavily shielded outer shell and a thin inner shell with a gas filled chamber in between the two shells. The radioactive source to be assayed is inserted in the center of the inner shell, and photon radiation penetrates the inner wall to produce ionization events inside the gas chamber. The primary difference between the activity calibrator and the air-communicating well chamber involves the gas within the chamber. The gas chamber of the activity calibrator is sealed and filled with pressurized argon. In order to maintain pressurization, the inner shell is thicker than that of air-communicating well chambers. This thicker shell greatly lowers the efficiency of the chamber for low energy photons, and no photons below 13 keV contribute to measurements made with the activity calibrator used in this work (Capintec 1990).

While the activity calibrator system functions similarly to the air-communicating well chamber system, the activity calibrator system is more convenient and expedient to use in a clinical setting. Because the gas chamber is sealed, the temperature and pressure within the chamber are not affected by small variations in atmospheric conditions in the room (Cherry 2003). Thus, there is no need for a thermometer and a barometer in normal climate controlled laboratory space. Also, the electrometer and ionization chamber are coupled within the activity calibrator. There is only one component to calibrate, and the displayed assay results do not need be adjusted, as the activity calibrator displays results

in units of activity. There is a risk of gas leaking from the chamber over time, which would cause inaccurate readings. Quality assurance performance tests should reveal any leakage that has occurred (Carey *et al.* 2012).

The activity calibrator displays assay results in units of activity (Bq or Ci), or apparent activity in the case of brachytherapy seeds. This is convenient for ^{125}I RSL seed assays for which apparent activity is used in written directives and other documentation. For brachytherapy dosimetry calculations, the displayed result must be converted to Air Kerma Source Strength (U) with equation 3.

reading (mCi) x 1.27 U/mCi = Air Kerma Source Strength (U) (3)

The ^{125}I brachytherapy seed vendor typically provides calibration data in both units.

Ionization Chamber Survey Meter

Ionization chamber survey meters, commonly referred to as exposure rate meters or dose rate meters, are based on the same underlying physics as the well-type ionization chambers. Given the survey meter's designed general purpose, portability and ruggedness take priority over accuracy (±10% at a specific calibrated energy) (Fluke 2013). The survey meter is a hand-held instrument and as such, must be made out of low-weight materials. It is not designed to envelope a radioactive source, but instead it is placed inside of a radiation field in order to measure the exposure rate for verification of safety and regulatory compliance. The chamber itself is much smaller than that of well-type ionization chambers. The electronics (voltage supply, electrometer circuit, batteries) are built into the same housing as the ionization chamber, and as such are also smaller

than the electronic components of well-type ionization chambers. Survey meter ionization chambers can also be pressurized for sensitivity to lower levels of radiation. In general, desirable fill gas properties are the same for both hand-held ionization chambers and well-type ionization chambers, and either air or a high-Z noble gas (typically argon) is used (Bushberg *et al.* 2002).

One of the challenges in using an ionization chamber survey meter for source assay procedures lies in utilizing a consistent geometry. For any calibration, the reproducibility of the geometry is necessary for accuracy. This is much easier with well-type ionization chambers, where the source is placed in the center of the well with a designated source holder. Thus, only one component must be placed accurately each time, and ideally the source holder is designed to slide in place with no room for variation. For the survey meter, both the meter and the source must be placed accurately utilizing a template, source holder, clamps, etc. The set-up must be carefully recreated for each future radioactive source assay. Thus, achieving acceptable accuracy and reproducibility in brachytherapy seed calibrations could be challenging when using an ionization chamber survey meter (Svensson *et al.* 1994).

An ionization chamber survey meter cannot be calibrated to display a reading in units of activity or other unit that can be directly converted to activity. Instead, the source exposure rate constant must be determined so that the displayed reading units of exposure rate in mR hr^{-1} (μSv hr^{-1}) can be converted to activity in units of mCi (GBq). Calibration of the survey meter then consists of determining a calibration factor for each radionuclide source, composition, form factor and geometry that will be assayed with the

survey meter. While it would not be practical to determine a calibration coefficient for general field use (varying radionuclides and constantly changing geometry), it is theoretically possible to create a consistent geometry for assaying a specific radioactive source (e.g. a brachytherapy seed).

NIST Traceability

The National Institute of Standards and Technology (NIST), founded in 1901 (originally named the National Bureau of Standards), provides standard weights and measurements for the United States (Cochrane 1974; Passaglia *et al.* 1999). NIST, along with similar institutions in other countries, provides an array of products and services that promote the consistent, accurate, and effective use of technology in research and industry (IAEA 2002). One vital service provided by NIST is the creation (via calibration, not actual source manufacturing) of reference standard sources for radiation measurements along with the framework (a calibration chain) for assuring calibration of radioactive sources and instruments for characterizing radiation is performed in a consistent, accurate, and reproducible manner. In this function, NIST is considered a Primary Standards Dosimetry Laboratory (PSDL). The Physical Measurement Laboratory (PML) provides radiation source and instrument calibration services that directly quantify their relationship to SI (Système International d'Unités) units with a specified uncertainty and confidence level. A source or instrument that has been calibrated at the NIST PML is said to have "direct NIST traceability" (Hendee *et al.* 2005). In practice, ionization chambers and other instruments and standards owned by end users are not calibrated by

NIST. Instead, they have been calibrated by a Secondary Standards Dosimetry Laboratory (SSDL). An SSDL receives calibrations of its standards and calibration instruments from NIST and must go through an accreditation process. The AAPM) is the accrediting body in the United States) before providing calibration services for end users. All of the SSDL sites must participate in regular intercomparison tests (Hendee 2005). The instruments and radiation sources calibrated by an SSDL are said to be secondary standards with calibrations directly traceable to NIST. Ionization chambers with directly traceable calibrations are recommended for calibration of radioactive brachytherapy seeds upon receipt from the seed vendor (Butler 2008). The source strength measurements will then have secondary traceability to NIST.

The system of SSDLs was developed by the AAPM in the 1970s to address several limitations with the previous method of contracting NIST directly. With the growing number of hospitals needing accurate and precise dosimetry calibration services, more laboratories were needed to meet the demand within a reasonable time frame. The SSDLs would be run independently from NIST (but with direct NIST traceability), and would focus on medical dosimetry calibration services. The SSDL system would be designed by AAPM to meet the needs of the medical physics community and to provide a technical resource for the AAPM. There are three SSDLs in the United States. They are given the title Accredited Dosimetry Calibration Laboratory (ADCL) and are accredited by the AAPM. One of the three ADCLs is housed within MDACC. The other two are at the University of Wisconsin and K&S Associates, Inc. in Nashville, Tennessee.

LITERATURE REVIEW

Nuclear Regulatory Commission (NRC)

Federal regulations relevant to the medical use of radioactive material are found in the code of federal regulations part 35 (10 CFR 35), Medical Use of Byproduct Material (U.S. NRC 2015c). Subpart G, Sealed Sources for Diagnosis, would appear to be a relevant section, but it is very brief and deals mostly with training and authorization. Subpart F, Manual Brachytherapy, gives a more thorough list of requirements and expectations for the use of sealed sources in patients. Section 35.400, Use of sources for manual brachytherapy, states that the regulations contained in 35.400 are intended for therapeutic use of sealed sources. While RSL procedures are not considered therapeutic, Subpart F provides the only relevant NRC requirements for radioactive seed source strength verification and dosimetry system requirements. Subpart K, Other Medical Uses of Byproduct Material or Radiation from Byproduct Material (10CFR35.1000), permits the RSL procedure (or any other sealed source use not covered in Subparts D-H) provided an application for such use has been submitted and approved by the NRC. According to the NRC Sealed Source and Device Registry, ^{125}I use for localization of nonpalpable lesions is explicitly authorized under 10CFR35.1000 (U.S. NRC 2015b).

BRACHYTHERAPY SEED CALIBRATION

Section 35.432, Calibration Measurements for Brachytherapy Sources, is the primary NRC reference for brachytherapy seed source strength verification. This section

requires the licensee to measure either the source strength or activity of the source by following “published protocols accepted by nationally recognized bodies” (U.S. NRC 2015c). These measurements must be performed with a dosimetry system that has been either calibrated with an appropriate NIST traceable source or calibrated by an ADCL within the previous 2 years. The licensee can extend this calibration period if multiple dosimetry systems are owned. In this case, the dosimetry system can wait 4 years for calibration as long as it has been inter-compared within 18-30 months of initial calibration with a second dosimetry system that has been calibrated within the previous 2 years and the dosimetry system (the system that is waiting 4 years for calibration) calibration factor has not changed by more than 2%. If these conditions are met, the original calibration factor (from actual NIST traceable calibration) will continue to be used. The air-communicating well-type ionization chamber is a commonly used brachytherapy dosimetry system that is calibrated according to this subsection of the federal regulations. Pressurized well-type ionization chambers, specifically designed for brachytherapy seeds, are also used for this purpose. The typical activity calibrator used by nuclear medicine departments is not designed specifically for brachytherapy seeds, and the calibration of such is governed by a different subsection of the federal code. The licensee is also allowed to use the source manufacturer’s calibration, provided the manufacturer used a dosimetry system with NIST traceable calibration or have seeds calibrated at an ADCL in lieu of performing in house calibration measurements.

The NRC Medical Licensee Toolkit (Licensing Guidance), Iodine-125 and Palladium-103 Low Dose Rate Brachytherapy Seeds Used for Localization of Non-

Palpable Lesions, specifically states that ^{125}I brachytherapy seeds used for RSL "are not regulated under 10CFR35.400 or the equivalent Agreement State regulations" (U.S. NRC 2015a). Instead they are regulated under 10CFR.1000 "Other medical uses". According to the Medical Licensee Toolkit, seed activity *will* be verified prior to administration with an instrument calibrated according to nationally recognized standards or manufacturer's instruction.

ACTIVITY CALIBRATOR

The pressurized well-type chamber, or activity calibrator, used by nuclear medicine departments for assaying unsealed byproduct material before it is administered to a patient, must also be calibrated and maintained in accordance with the regulations. This is stated in Subpart C, General technical requirements, but the process for doing so is not given. Instead the licensee is instructed to "calibrate the instrumentation in accordance with nationally recognized standards or the manufacturer's instruction" (10CFR35.60).

A recommended model activity calibrator calibration procedure is described in the NRC Regulatory Guide 10.8, Guide for the Preparations of Applications for Medical Use Programs. The model procedure given in Appendix C of NRC Regulatory Guide 10.8 is essentially a full quality control (QC) program as opposed to a one-time calibration. The model procedure consists of daily constancy tests, quarterly linearity tests, geometry at installation, and annual accuracy tests. Although the regulatory tolerances are ±10% (for each of the tests), Regulatory Guide 10.8 recommends setting an internal procedural

tolerance at ±5% in order to facilitate corrective actions before approaching regulatory tolerances (ANSI 1986; U.S. NRC 2008).

IONIZATION CHAMBER SURVEY METER

The regulatory requirements for survey meter calibration are covered in 10CFR35.61. Note that these instructions are for general survey meter use, and will not be sufficient for the purpose of brachytherapy source strength verification. Survey meters must be calibrated before first use, annually, and after repairs. The calibration process for survey meters leaves a lot of room for error. Two calibration points are chosen per scale. The survey meter is adjusted so that the reading is close to the expected, theoretical response at the two points. The difference between the indicated reading and the theoretical calculation must be less than 20% for each calibration point.

NRC Regulatory Guide 10.8 gives more specific instructions within the Appendix B model survey meter calibration procedure. The calibration source must be a NIST traceable point source with no more than 5% uncertainty. The source should emit radiation of the same type and similar energy to that of the radiation field in which the detector will be used, and should be of sufficient strength. Regulatory Guide 10.8 recommends a more conservative error margin of 10% for any one particular calibration point. Also, for digital readout survey meters that automatically rescale, only one calibration point is needed for each decade, and two calibration points are needed on at least one decade. Recommended daily QA checks only include constancy tests, which consist of taking an exposure rate reading with a known check source that was also measured at the time of calibration.

Department of State Health Services (DSHS)

Texas state regulations relevant to medical radioactive material are found in the Texas Administrative Code part 289.256 (25TAC289.256), Medical and Veterinary Use of Radioactive Material (DSHS 2015). The wording is essentially verbatim from the NRC regulations for all aspects of low dose rate manual brachytherapy seed strength verification. Subsections 289.256(rr)-289.256(ww) give the requirements and expectations for the use of manual brachytherapy sources in patients. Subsection 289.256(rr), Use of Sealed Sources for Manual Brachytherapy, states that the regulations contained within 289.256(rr) are intended for therapeutic use of sealed sources. While RSL procedures are not considered therapeutic and as such, this application is should fall under regulations analogous to NRC 10CFR35 Subpart K, Other Medical Uses of Byproduct Material or Radiation from Byproduct Material (10CFR35.1000), subsections 289.256(rr)-289.256(ww) provide the only relevant DSHS regulations for radioactive seed source strength verification and dosimetry system requirements. No analogue to 10CFR35.1000 exists in the DSHS regulations, but there is reference to the Sealed Source and Device Registry, which lists localization of nonpalpable lesions as an authorized use (governed by NRC regulations) of ^{125}I brachytherapy seeds.

BRACHYTHERAPY SEED CALIBRATION

Subsection 289.256(ww), Calibration Measurements of Brachytherapy Sealed Sources, is the primary reference for brachytherapy seed source strength verification. This section requires the licensee to measure either the source strength or activity of the

source by following “published protocols accepted by nationally recognized bodies”. These measurements must be performed with a dosimetry system that has been either calibrated with an appropriate NIST traceable source or by an ADCL within the previous 2 years. The licensee can extend this calibration period if multiple dosimetry systems are owned (and kept in calibration) by following the same steps outlined in the NRC Code of Federal Regulations.

The DSHS Regulatory Guides do not provide any information specific to RSL procedures. There is a Regulatory Guide for medical licensees titled Regulatory Guide 3.1 – Guide for the Preparation of License Applications for the Medical Use of Radioactive Material (DSHS 2012). It is very similar to the NRC Regulatory Guide 10.8. There is no DSHS analogue to the NRC Medical Licensee Toolkit for RSL. Without any specific DSHS regulations to address RSL procedures, licensees much follow the NRC guidelines.

ACTIVITY CALIBRATOR

The pressurized well-type chamber, or activity calibrator, used by nuclear medicine departments for assaying unsealed radioactive material, must also be calibrated and maintained in accordance with the regulations, and the general requirements for this process are explained in subsection 289.256(v). The calibration must be performed in accordance with nationally recognized standards or manufacturer’s instructions. This section of the regulations specifically requires a minimum of tests for accuracy, constancy, linearity, and geometry dependence. An ongoing QC program is also required. Accuracy must be performed once per year, constancy daily before use,

linearity quarterly, and geometry dependence at installation and after relocation and repair.

Regulatory Guide 3.1 – Guide for the Preparation of License Applications for the Medical Use of Radioactive Material recommends that the licensee follow ANSI, NRC, or manufacturer's instruction. A recommended model activity calibrator calibration procedure is described in Appendix I of Regulatory Guide 3.1. It is essentially the same model procedure given in the NRC Regulatory Guide 10.8. The model procedure is a full QC program as opposed to a one-time calibration. The model procedure consists of daily constancy tests, quarterly linearity tests, geometry at installation, and annual accuracy tests. As was the case with the NRC, the regulatory tolerances are ±10%, Regulatory Guide 3.1 recommends setting an internal procedural tolerance at ±5% in order to facilitate corrective actions before approaching regulatory tolerances.

IONIZATION CHAMBER SURVEY METER

The regulatory requirements for survey meter calibration are covered in 289.256(w). This subsection is verbatim from NRC 10CFR35.61. Survey meters must be calibrated before first use, annually, and after repairs. Two calibration points are chosen per scale. The survey meter is adjusted so that the reading is close to the expected, theoretical response at the two points. The difference between the indicated reading and the theoretical calculation must be less than 20% for each calibration point. Regulatory Guide 3.1 does not provide a model survey meter calibration process.

American Association of Physicist in Medicine

"The AAPM is a scientific and professional organization, founded in 1958, composed of more than 8000 scientists whose clinical practice is dedicated to ensuring accuracy, safety and quality in the use of radiation in medical procedures such as medical imaging and radiation therapy. One of the primary goals of the AAPM is the identification and implementation of improvements in patient safety for the medical use of radiation in imaging and radiation therapy" (AAPM 2015). The AAPM is a nationally recognized body that regularly publishes recommended procedures and protocols in the form of AAPM Reports. There are six reports that provide recommendations of interest for this work (i.e. brachytherapy seed, well chamber and ionization survey meter calibration and quality assurance).

BRACHYTHERAPY SEED SOURCE STRENGTH VERIFICATION

The first published recommendations for brachytherapy seed source strength calibration are printed in AAPM Report #13, Physical Aspects of Quality Assurance in Radiation Therapy. In this report, brachytherapy seed calibration by intercomparison with a standard source is emphasized over relying on the seed manufacturer's calibration or instrument calibration factor (Svensson *et al.* 1984). Furthermore, the report does not give preference to any particular instrument type, as long as the same instrument is used for each seed calibration. The activity calibrator typically found in nuclear medicine departments is listed as a perfectly acceptable instrument for this purpose. Regardless of chosen instrument the measurement reproducibility should be within ±2%. The user

should characterize the instrument in terms of scale factor and linearity of all scales or radionuclide settings that might be changed for different seeds, ion collection efficiency, geometry and length dependence, thickness, and energy dependence.

In the source intercomparison process, one source from a manufactured lot to be used in a clinical setting is chosen to be the standard source. This standard source is sent to an ADCL for calibration. (The ADCL is not actually mentioned in Report #13. Instead the National Bureau of Standards, the predecessor of NIST, is referenced.) Once the standard source has a NIST traceable calibration, it is placed in the clinic's calibration instrument in the same geometry as the other clinical sources. The readings are compared in order to determine the activity (source strength or Air Kerma Strength) of all sources. The NIST traceable calibration source can also be used for ongoing instrument quality assurance tests. When the radionuclide would require frequent replacement due to a short half-life, additional steps must be taken in order to facilitate future seed batch calibration after the standard source has decayed. After the standard source has been calibrated at an ADCL, the calibration must be transferred to a long-lived reference source. AAPM Report #13 recommends two different methods of accomplishing the calibration transfer (Svensson *et al.* 1984). In the first method the instrument is calibrated with the standard source. The reference source is then assayed with the instrument and used as a QA source before each subsequent seed calibration. In the second method both reference and standard sources are assayed in the instrument, and the ratio of the instrument responses is used to calculate a correction factor in terms of the reference source.

AAPM Report #46, Comprehensive QA for Radiation Oncology, written 10 years later, updates and supersedes AAPM Report #13 (Kutcher *et al.* 1994). This report also emphasizes independent verification of source strength of brachytherapy seeds prior to administration in a patient. It is recommended that this calibration be accomplished through a procedure having either direct traceability (source calibrated by NIST or an ADCL) or secondary traceability (intercomparison with a directly traceable source of the same design or source calibration with a directly traceable instrument). The discrepancy for a batch should not be greater than 3% on average and not greater than 5% for a single source. The ideal calibration instrument measurement reproducibility is better than 2%, and the activity calibrator (well chamber) is given as an appropriate instrument. Again the user should characterize the instrument in terms of scale factor and linearity, ion collection efficiency, geometry and length dependence, thickness, and energy dependence. A calibration/QA redundancy system consisting of instrument and source intercomparison is also introduced in Report #46. One example is a three-component redundancy system consisting of the seed calibration instrument, a standard source of the same radionuclide that will be calibrated with the instrument, and a second long-lived standard source of a different radionuclide. The intercomparison redundancy check is performed each time a seed is calibrated. Report #46 recommends a three-components system, although two-component systems are allowed.

AAPM Report #51, Dosimetry of Interstitial Brachytherapy Sources, serves primarily to give the medical physicist a dose calculation formalism for interstitial brachytherapy. Report #51 emphasizes source strength measurements be made in units

of Air Kerma Strength, but it does not make any recommendations relating to the actual calibration process itself. AAPM Report #59, Code of Practice for Brachytherapy Physics, repeats the source strength calibration recommendations from Report #46 but with use of the word "shall" when referring to verification of manufacturer source calibration with secondary (or direct) traceability. This indicates a legal requirement that a licensed medical physicist performs this task for each source (or a single sample from a batch) before administration in a patient (Nath *et al.* 1997). The next AAPM Report that discusses brachytherapy source calibrations, AAPM Report #84, Update of AAPM Task Group No. 43 Report: A Revised AAPM Protocol for Brachytherapy Dose Calculations, reiterates previous brachytherapy source calibration recommendations, but it never uses the word "shall" in regards to secondary traceability. Instead "recommends" and "should" are used (Rivard *et al*. 2004). AAPM Report #98, Third-Party Brachytherapy Source Calibrations and Physicist Responsibilities: Report of the AAPM Low Energy Brachytherapy Source Calibration Working Group, summarizes the various AAPM reports regarding brachytherapy source calibration and addresses the practice of allowing a third-party (not the source manufacturer or end user) to calibrate the brachytherapy source. Essentially, AAPM Report #98 reinforces AAPM Report #59. The institution administering brachytherapy seeds into patients is expected to verify the manufacturer source calibration using a system with secondary traceability. The words "shall" and "must" are used in regards to secondary traceability, which indicates requirements for regulatory compliance. AAPM Report #98 places responsibility for source strength calibration to the institutional (administering brachytherapy seeds to patient) medical

physicist regardless of any third-party brachytherapy source calibration that has been performed.

WELL CHAMBER CALIBRATION AND QA

The first AAPM-recommended brachytherapy source calibrator QA program appears in AAPM Report #46. Specific QA tests, tolerances and frequencies are listed for the ionization well chamber. There are two categories of testing frequencies: 1. initial use or following malfunction and repairs, and 2. each use or ongoing evaluation. The first category includes ADCL calibration (directly traceably to NIST), precision, linearity, collection efficiency, geometry, energy dependence. The second category includes redundant checks and tests for leakage of pressurized chamber gas. The recommended tolerance is 1% coefficient of variation for linearity and collection efficiency, and it is 2% coefficient of variation for precision and redundant checks. All other tolerances simply require documentation and application of a correction factor. For the redundancy checks, a three-component redundancy system is preferred (Kutcher et al. 1994).

AAPM Reports #59, #84 and #98 support the same well chamber QA program outlined in AAPM Report #46. AAPM Report #84 also gives two different calibration schemes that assure secondary traceability. In the first scheme, the well chamber is sent to an ADCL (on two year intervals) for a directly traceable calibration. Alternatively, a source calibrated by NIST or an ADCL (directly traceable source calibration) can be used to calibrate a well chamber, giving it a calibration with secondary traceability. In either method, this well chamber can then be used to verify the manufacturer calibration of a

brachytherapy source. It is recommended that the user verify that the total uncertainty in the well chamber calibration (secondary traceability) is comparable to that of a directly traceable well chamber calibration (Rivard *el al.* 2004).

RADIONUCLIDE CALIBRATION AND WELL CHAMBER CALIBRATION AND QA IN DIAGNOSTIC IMAGING

AAPM Report #181: Selection, Use, Calibration, and QA of Radionuclide Calibrators in Nuclear Medicine, is the only AAPM report that gives a full treatment to well chamber radionuclide measurements in a nuclear medicine (therapy and diagnostic) setting. Although most nuclear medicine radionuclide doses are in unsealed form, it is relevant to consider the acceptable levels of uncertainty, as this represents the most common example of non-therapeutic radionuclides being administered to a patient. The report refers specifically to pressurized well-type ionization chambers commonly referred to as radionuclide or dose calibrators. AAPM Report #181 recommends that assay activities be ±10% (total uncertainty budget) of prescribed activities for diagnostics (Carey *et al.* 2012). For short lived, unsealed radioactive material such as technetium-99m ^{99m}Tc and fluorine-18 ^{18}F uncertainty in exact administration time and amount of drug that is delivered internal to the patient's body, along with calibration accuracy, contribute to total uncertainty in administered dose. In the case of sealed radioactive material (e.g. ^{125}I brachytherapy seeds) the uncertainty in calibration accuracy and implant location are the primary sources of uncertainty. A "properly calibrated, operated, and maintained" activity calibrator should provide assays within acceptable accuracy

tolerances. Note that AAPM Report #181 recommends not using a radionuclide activity calibrator for sealed sources that will be used for brachytherapy. The report references AAPM Report #98 for this statement, but no equivalent statement exists in Report #98. AAPM Report #98 only states that "the institution shall have a system for measuring source strength with secondary traceability for all source types used in practice" (Butler et al. 2008).

AAPM Report #181 offers a well chamber calibration scheme that is more flexible than that of well chambers used for brachytherapy seed calibration. Unlike well chambers used for sealed brachytherapy sources, activity calibrators are usually given a factory calibration with specific calibration coefficient settings (referred to as cal numbers) for a range of commonly used radionuclides in a specific geometry, as well as source composition and form factor. The factory calibration scheme starts with a master well chamber calibrated with a few NIST traceable sources. From these standard source assays, a response-energy curve is created, and calibration settings are determined for other radionuclides based on interpolation or Monte Carlo simulation. The calibration is then transferred to the production well chambers that are purchased and used by medical facilities, nuclear pharmacies, etc. The end user can perform a calibration of the well chamber as well using an appropriate NIST traceable standard. AAPM Report #181 references three classes of well chamber calibration, the secondary standard radionuclide calibrator (SSCR), the reference radionuclide calibrator (RRC) and the production radionuclide calibrator (field instrument). The difference lies in the traceability pathways and use. The SSCR is calibrated with a primary NIST traceable standard and is used to

calibrate secondary standard sources that are then used to calibrate field instruments (Zimmerman *et al.* 2000). If a field instrument is later calibrated with a NIST traceable standard source, then it can become a SSCR. The RRC calibration has secondary traceability and is also used to calibrate field instruments, but it is not used to calibrate secondary standards (nor is it used in the field). The recommended activity calibrator assay accuracy tolerance for low energy photon emitters (<100 keV) is 10% with field instruments and 5% with SSCR and RRC.

During the well chamber calibration process, changes and adjustments are not made to the well chamber itself (unless repair is needed). Instead, a standard source is assayed with the well chamber, the response is recorded and a calibration coefficient is calculated in order to account for the difference between well chamber response (displayed on instrument direct readout or electrometer) and actual source activity. This calibration coefficient is then applied to all future measurements of the same source type (radionuclide and physical design). When working with activity calibrators, the instrument performs the calculations and automatically assigns varying calibration coefficients to a series of calibration settings (cal numbers). The user simply presses a button to change the calibration setting until the displayed activity matches the actual activity of the standard source. This calibration setting is then selected for all future measurements of the same source type (radionuclide, geometry, etc.). Even with a calibrated well chamber, there are several additional sources of error. One common error occurs when the assayed source geometry (location, encapsulation/container material/ size/volume) differs from that of the primary standard. Then the assigned calibration

setting could potentially yield inaccurate results. Other sources of error include errors in calibration of standard sources, variation in chamber gas pressure, backscatter within the well, and the accuracy and linearity of the system electronics (Carey *et al.* 2012). Activity calibrators tend to be less accurate when used to assay low-energy (<100 keV) photon emitters, such as ^{125}I. In this energy range, photon attenuation in the source holder and inner well chamber wall is much greater and more dependent on variation in material.

Recalibration recommendations vary with well chamber manufacturers. Typically this occurs after damage and repairs, long periods of not being in use, or when the instrument fails a QA test, although periodic recalibration is recommended, in general, in order to maintain optimal performance. The QA program recommended in AAPM Report #181 includes 11 performance tests; physical test, system electronics test, clock accuracy, high voltage, zero adjust, background response/contamination check, check source (constancy and relative instrument response), accuracy test, reproducibility (precision), system linearity, and supplier equivalence (Carey *et al.* 2012). All 11 tests should be performed during acceptance, annually and after repair. All tests except for accuracy, reproducibility, system linearity, and supplier equivalence should be performed daily, with these four being performed at least annually.

DESCRIPTION OF HOW PROBLEM WAS SOLVED

^{125}ISeed Calibration

Eight total ^{125}I interstitial brachytherapy calibration seeds (model number IAI-125A, IsoAid, 7824 Clark Moody Boulevard, Port Richey, FL 34668) were calibrated for use in determining the appropriate (for this specific type of ^{125}I source) activity calibrator activity assay setting (calibration number) and survey meter calibration factor, and for assessing the associated uncertainty in ^{125}I seed assays made with these radiation detection systems. Each seed was manufactured and calibrated by IsoAid as part of a RSL seed lot for use in clinical RSL procedures at MD Anderson. Initially, the six most recent (highest activity) available seeds were chosen, and two additional seeds were added midway through the project when new RSL seed lots arrived. One of the original vendor calibration certificates is shown in Appendix A. The ^{125}I seed with the highest activity (from original group of six, excluding the seventh seed) was sent to the MDACC ADCL for a NIST traceable calibration. The ADCL calibration was in units of Air Kerma Strength (U), and it was necessary to divide this value by the conversion factor 1.27 U mCi^{-1} (for ^{125}I seeds) to obtain the apparent activity in mCi (Nath *et al.* 1995). The seeds were also examined for anisotropy in a qualitative fashion with a survey meter and the effect of which was tested on the well chamber to determine if anisotropy (if observed) would alter outcome of the seed calibration. The test on the well chamber consisted of assaying Seed 1 in the HDR1000 for 20 trials of 15 s each and repeating the process with the seed rotated ~90˚. Only the seed was rotated, not the seed holder. The accumulated

charge (pC) for each set of trials was compared in terms of maximum reading, minimum reading, percent difference between maximum and minimum, average reading, standard deviation and coefficient of variation.

Only one seed (referred to as "Seed 1" from here on) received an ADCL calibration. The other six seeds were each calibrated with an air-communicating well-type ionization chamber (model HDR1000, Standard Imaging Inc., 3120 Deming Way Middleton WI 53562). In order to obtain the HDR1000 calibration coefficient in units mCi pA^{-1} for ^{125}I seeds (specifically for IsoAid M/N: IAI-125A) and determine the optimal counting time to assure satisfactory levels of uncertainty, Seed 1 was assayed a total of 60 times. Three sets of 20 assays were performed with charge collection times of 15 s, 30 s, and 60 s. Each set of 20 assays was grouped into subsets of 5, 10, and 20 measurements and averaged in order to investigate the effect of number of trials on precision (i.e. the average of 5 trials vs. the average of 10 trials vs. the average of 20 trials). This sums to a total of 21 measurement data permutations (four sets of five trials, two sets of 10 trials and one set of 20 trials for each count time of 15 s, 30 s and 60 s) within the 60 total individual measurements. Once the well chamber calibration coefficient was determined, the well chamber was used to assay the other five seeds. The same procedural combination of 60 measurements was used to assay each of the five seeds and analyze the precision and reproducibility of this process for the various combinations of experiment parameters. The entire seed calibration process (except the initial Seed 1 ADCL calibration) was repeated two more times on different days in order investigate procedural reproducibility in terms of both time and seed radioactive decay.

On each day, a barium-133 (^{133}Ba) source was used to perform a constancy check of the HDR1000. Five well chamber calibration coefficients (obtained from assays of Seed 1 on five different days) were compared to the original ADCL calibration of the well chamber (May 2014) and differences tested for statistical significance. The first calibration coefficient obtained with the first day of Seed 1 measurements was used throughout this work in all subsequent apparent activity measurements.

Activity Calibrator Calibration

The activity calibrators commonly used by nuclear medicine clinics are designed for assay of unsealed radioactive material in a vial, syringe or capsule. While these instruments are capable of measuring the radiation emitted from sources of various shapes and forms (solid, liquid, gas), they do not come with any standard apparatus for positioning a brachytherapy seed in a consistent geometry. For this investigation, two different geometry configurations were created. The first configurations consisted of the source holder from the HDR1000 and one of the vial/syringe inserts, commonly referred to as “dippers”, that came with the activity calibrator (CRC-15R, Capintec, Inc., 6 Arrow Road Ramsey, NJ 07446) used in this investigation. The seed was placed in the HDR1000 single seed holder (model 70016, Standard Imaging Inc., 3120 Deming Way Middleton WI 53562), which was then inserted into the dipper. The second geometry configuration consisted of the dipper and the ~7.5 ml glass vial that the seed was shipped in. The seed was randomly placed on the bottom of the vial, and the vial was placed at the bottom center of the dipper. Both geometry configurations are shown in Figure 2.

Whereas it was not possible for the ^{125}I seed to move significantly inside the HDR1000 single seed holder, the seed could easily slide to various positions on the bottom of the glass vial. The seeds were 4.5 mm in length, and the bottom of the glass vial was circular with an inner diameter of 14 mm. Measurements were also performed with a second dipper and glass vial to assess reproducibility with regards to system parts that are likely to be exchanged over time. On two separate days, each seed was placed in the activity calibrator utilizing the two geometry configurations described above. The cal number was varied until the correct apparent activity was displayed. Each cal number and apparent activity was recorded. The process was repeated with a second glass vial, a second dipper and a second HDR1000 single seed holder, and the same cal numbers (correct and incorrect) were selected.

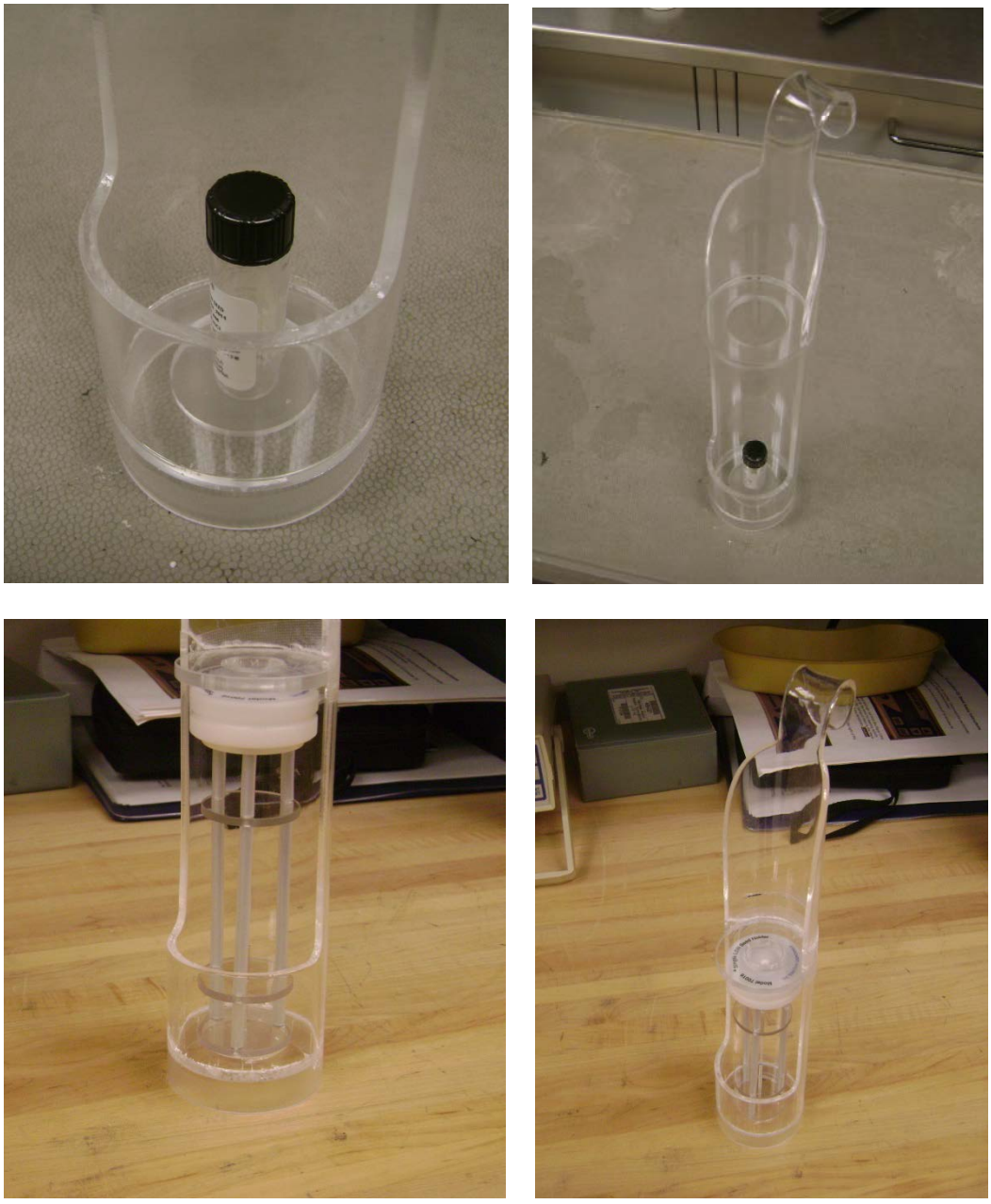

Figure 2. Geometry configurations for the glass vial and the HDR1000 single seed holder. The dippers were then slid into the activity calibrator.

In order to assess uncertainty in ^{125}I seed assay results due to inconsistent measurement geometry, an experiment was devised in which seed assays were performed under conditions of consistent (as much as possible) geometry and intentionally inconsistent geometry. For the case of consistent geometry, Seed 1 was inserted into the activity calibrator 25 times (five sets of five trials) per geometry configuration (50 total trials) with attention paid to accurately reproducing the geometry each time. For each set of five trials the glass vial or HDR1000 single seed holder was placed in the center on the bottom of the activity calibrator dipper. Tape was used to assure that the geometry did not change in between trials. After every five sets of insertion/removal of the seed, the geometry configuration was taken apart and reassembled to investigate the reproducibility of this "consistent" geometry configuration. For each trial the cal number was varied until the correct apparent activity was displayed.

For the case of inconsistent geometry, Seed 1 was then inserted into the activity calibrator 35 times per geometry configuration while the location of the glass vial or HDR1000 single seed holder was intentionally shifted to various off-center locations on the bottom of the activity calibrator dipper between each trial. Seven different specific locations were chosen, and each set of seven trials was repeated five times. The locations are shown in Figure 3. For each trial the cal number was varied until the correct apparent activity was displayed. The maximum and minimum cal numbers were identified for each set of seed measurements (consistent geometry and inconsistent geometry). These cal numbers were then used to assay the seed. For each cal number the seed was assayed five times and averaged. The percent difference between the apparent activity results

from consistent geometry and inconsistent geometry were calculated as well as the percent error in the apparent activity results obtained from the maximum and minimum cal numbers for both consistent geometry and inconsistent geometry.

Figure 3. The seven glass vial locations in this experiment included the offset location shown, three other offset locations at 90° intervals, the glass vial lying horizontally, as shown, the glass vial lying horizontally, but rotated 90° and a centered, upright position (as in the "consistent geometry" configuration). The four 90° offset locations and the centered, upright-position were also utilized for the HDR1000 single seed holder. The horizontal positions were not possible due to the height of the seed holder.

All seven seeds were used to determine an appropriate cal number for the activity calibrator. Utilizing both geometry configurations under conditions of "consistent" geometry as described earlier, Seed 1 was measured on five different days spanning a period of six weeks to determine an appropriate cal number. For each measurement, four different apparent activity values were utilized. The ADCL calibration was considered the most accurate and was thus assumed to be the true apparent activity of the seed. The vendor provided apparent activity was utilized for the purpose of comparison (and in practice, after verification of seed apparent activity, it is the vendor stated apparent activity value that is actually used for comparison). For both of these cases, the apparent activity values were decayed to the exact time of measurement (to the minute). The last two apparent activity values were based on the vendor provided apparent activity but under the assumption that the calibration time was only accurate to the nearest day instead of minute. This was done to assess the variation in cal number (and final ^{125}I seed assay) that might arise from only entering the vendor calibration and experimental measurement days (and not including the hour or minute) into the calculation spreadsheet. To account for this, the vendor calibration time was offset by ±12 hr, which represents a reasonable worst case. Although, in theory the time could be off by up to 24 hr, the extremes (i.e. vendor calibration very early in the morning and institution assay late at night or vice-versa) were considered unlikely to occur in practice. For each apparent activity value, the activity calibrator cal number was varied until the correct apparent activity appeared on the display. This resulted in eight calibration numbers (four per geometry configuration) per seed per day, or 32 total calibration numbers (with

many duplicate calibration numbers) per seed. This process was then repeated for each of the six other seeds also over a period of two months. Constancy tests were performed periodically with a ^{137}Cs vial source for one month and then later with an ^{125}I seed over a period of one month. The activity calibrator also received independent constancy tests and an annual accuracy test, which can be found in Appendix B.

The various activity calibrator cal numbers were examined in order to identify significant sources of uncertainty. Each procedural step was applied separately to the glass vial geometry configuration and the HDR1000 seed holder geometry configuration. It was not reasonable to have an intercomparison between the cal numbers for the two geometry configurations, as the activity calibrator response is highly sensitive to geometry difference. For each seed apparent activity (experimental or ADCL calibration, vendor calibration, vendor -12 hr, vendor +12 hr) the minimum and maximum cal numbers were identified and the mean cal number was calculated (and then rounded to whole number since fractional cal numbers do not exist). The standard deviation of the cal numbers was calculated, which allowed cal numbers to be identified at $\pm 1\sigma$ and $\pm 2\sigma$ from the mean. For each ^{125}I seed the percent difference between the maximum and minimum cal numbers (based on experimental or ADCL ^{125}I seed calibration) over the five trials was also calculated.

While variation in activity calibrator cal number is interesting to consider, the ultimate goal of this project is to assess the ability of a activity calibrator to accurately assay unknown ^{125}I seeds. In order to quantify this, Seed 1 through Seed 4, Seed 7, and a new seed, Seed 8 (replaced the oldest seed, Seed 6, due to low activity), were assayed in

the activity calibrator over the various ranges (mean, maximum, minimum, ±1σ and ±2σ from the mean) of cal numbers identified in the results from previous procedures. The percent error was calculated for each resulting apparent activity data point. The percent error data were then grouped across all ^{125}I seeds and assay days by original seed calibration method (experimental or ADCL calibration, vendor calibration, vendor -12 hr, vendor +12 hr) and the mean, standard deviation and 95% CI were calculated for these groups. The same statistical parameters were also considered for each individual seed over the five assay days. The total uncertainty (uncertainty budget) from all steps up to this point was calculated for each empirically determined ^{125}I seed apparent activity.

Ionization Chamber Survey Meter Calibration

The ionization chamber survey meter (451B, Fluke Biomedical, 6920 Seaway Blvd, Everett, WA 98203) does not have a dedicated mechanism to maintain a consistent geometry. In order to ensure consistent geometry, a template was made with designated locations outlined for the survey meter and for the seed. This setup is shown in Figure 4. Geometry configurations incorporating the same glass vial and HDR1000 single seed holder as in the activity calibrator procedures were used. First, the seed was placed in the HDR1000 single seed holder, which was then placed on top of the small lead shipment container in order to elevate the seed so that it was approximately in line with the center of the ion chamber entrance window. For the second geometry the seed was placed in the glass vial, which was then placed on top of a cube shaped piece of foam.

There were two main concerns with regard to geometry reproducibility. The first potential source of error was distance between the seed and chamber window. In order to assess the relevancy of this source of error, the seed (in vial/holder on top of elevation device) was moved in 2 mm increments from 30 cm to 29.2 cm, and five exposure rate measurements were recorded and averaged at each distance. This process was repeated five times with the geometry being disassembled and reassembled after each set. The second potential source of error considered was rotation of the seed. Unlike the well chamber and activity calibrator, a survey meter does not envelope the seed. Thus, an anisotropic radiation field will not be accurately measured with a survey meter. For both geometries, the seed, vial and elevation device were rotated in 90º intervals with five exposure rate measurements recorded and averaged at each interval. This process was repeated five times with the geometry configuration being disassembled and reassembled after each set.

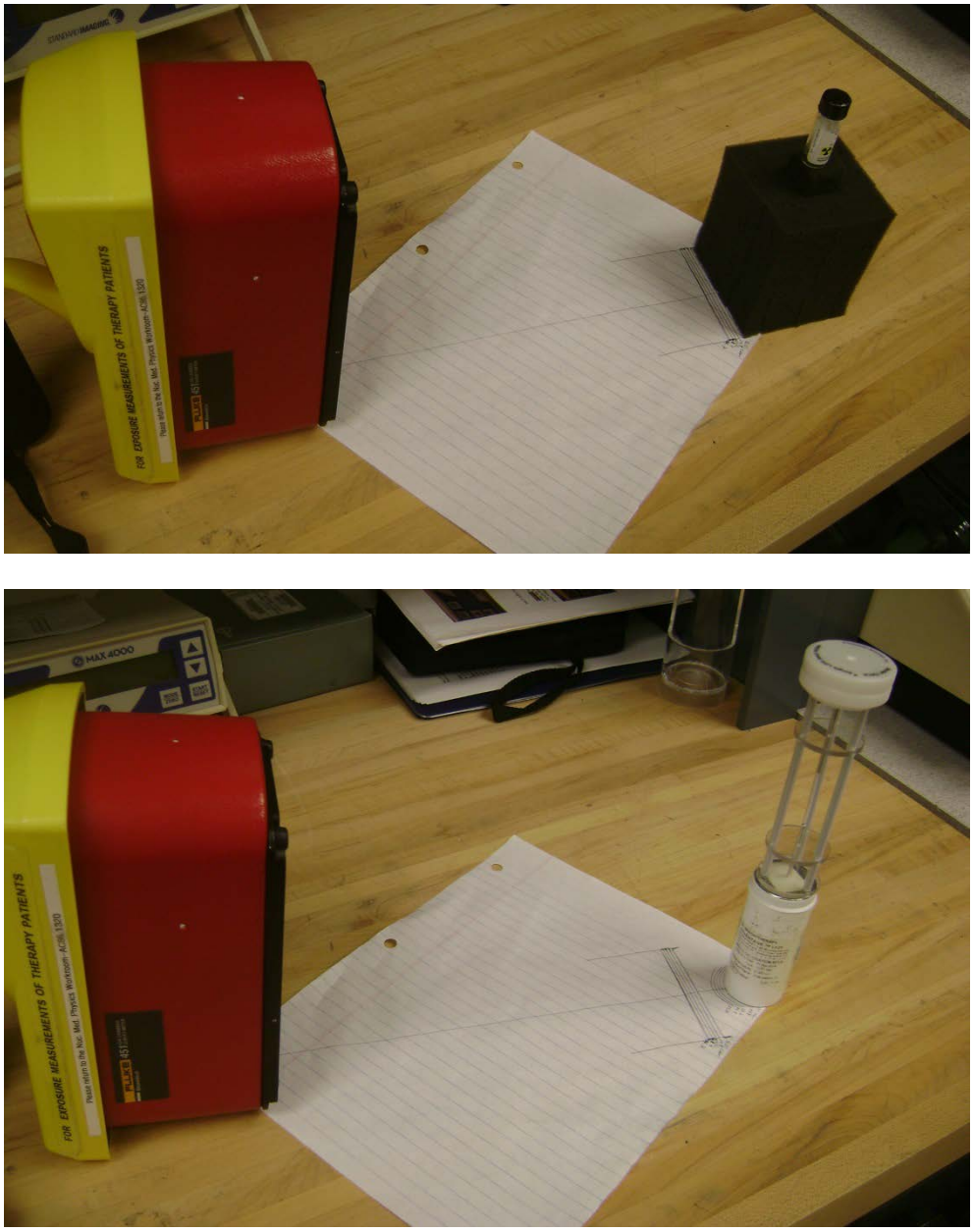

Figure 4. Ionization chamber survey meter measurement geometry configurations for both the glass vial and HDR1000 single seed holder. The 2 mm offset lines can be seen on the template for both geometry configurations.

Only Seed 1 and Seed 7 were used to determine the calibration factor in units of mR hr^{-1} mCi^{-1} (μSv hr^{-1} GBq^{-1}) for the survey meter. The calibration factor was calculated for each exposure rate data point in two sets, one utilizing the ADCL and experimental HDR1000 seed calibration and the other set using the vendor calibration. Calibration factor uncertainty was calculated with respect to three different sources of error. The first two sources of error were the potential geometry errors discussed earlier (source to detector distance and variation when source is rotated), and the third source of error was variation in detector response and recording methods. Ionization chamber survey meters do not typically settle on one stable exposure rate reading, and the procedures for recording data must account for this variation. Thus the use of five exposure rate measurements recorded over short time intervals and averaged to create one data point. Uncertainty due to errors in source-to-chamber distance was assessed by analyzing the calibration factors at varying distances for the same seed, on the same day. Variations in geometry assembly, chamber response and data recording methods were assessed by analyzing the calibration factors across the five sets of trials for the same seed, on the same day, at the same source-to-chamber distance. Initially, the entire survey meter calibration process was to be repeated four more times on different days in order to investigate procedural reproducibility in terms of both time and seed radioactive decay. Instead the process was repeated only once because variation in calibration factors was unacceptably high on both days.

From the set of calibration factors, minimum and maximum calibration factors were identified, and the mean calibration factor and calibration factors at $\pm 1\sigma$ and $\pm 2\sigma$

from the mean were calculated for both Seed 1 and Seed 7. The calibration factors were derived from four sets of data per geometry configuration, one set based on the experimental and ADCL calibrations with no variation in source-to-chamber distance, and one set based on the experimental and ADCL calibrations with variation in source-to-chamber distance. The other two sets were the same, except the vendor stated seed calibration was used. Utilizing the eight sets of calibration factors, Seed 7 and Seed 8 (the only seeds with activity high enough to be calibrated with a survey meter at this point in the experiments) were measured 20 times, and the average exposure rate was converted to apparent activity. Each of the 20 Seed 7 and Seed 8 data points were the mean of five exposure rate measurements taken in the same manner as earlier to account for the inherent variation in ionization chamber survey meter readings. The percent error was calculated for each apparent activity value. Note that the HDR1000 single seed holder was positioned such that its support pillars were not between the seed and the chamber window.

RESULTS

ADCL ^{125}I Seed Calibration

The apparent activity of Seed 1 was 0.1303 mCi (4.82 GBq or 0.1655 U) @ 12/24/2014 10:49 AM, per ADCL calibration. During the ADCL calibration, the seed was flipped end-over-end (180º) for half of the measurements, and there was a 0.1065% difference in the mean of the two sets of measurements. There was no evidence of ^{125}I seed anisotropy (with the length of the seed as the axis of rotation) when Seed 1 was tested qualitatively with a survey meter (the meter reading did not change with seed rotation) and assayed with the well chamber. The results of the well chamber anisotropy test are shown in Table 1. For the ionization chamber survey meter, there were other geometric problems with rotating the seed, which overshadowed any effects cause by inherent ^{125}I seed anisotropy. This resulted in instrument reading variations of greater than 60% with the HDR1000 single seed holder geometry configuration and greater than 100% with the glass vial geometry configuration.

Table 1. Results from ^{125}I seed anisotropy tests. HDR1000 accumulated charge measurements with Seed 1 for 20 trials at 15 s intervals. Note that the seed rotation was about the longitudinal axis.

HDR1000	Non-rotated	Rotated ~90°
Max (pC)	-10.80	-10.80
Min (pC)	-10.97	-10.98
Max/Min % diff	1.6%	1.7%
Mean (pC)	-10.86	-10.89
std dev (pC)	0.0394	0.0445
CV	0.36%	0.41%

Well Chamber Calibration Coefficient

For each round of measurements (accumulated charge) made with the well chamber, several different combinations of charge collection times and number of trials were employed. In general, varying between the averages of 5-trial, 10-trial and 20-trial measurement sets showed little statistical variation. Assuming the 20-trial set to be the most accurate measurement of mean accumulated charge, two-tailed t-tests (mean of 20-trial set used as theoretical mean) were performed on the 5-trial sets and 10-trial sets for each time interval (15s, 30s, 60s). The results of the t-tests showed that the data in each set were not statistically different (95% CI) than the 20 trial set. This held true for all seeds on every calibration round. There was slightly more variation in the average charge accumulation within the 5 trial sets, as the percent difference between maximum and minimum values and the coefficient of variation were slightly higher. Both of these statistical parameters increased with decreasing seed activity, ranging between <0.1% to 3.1% and <0.1% to 1.31%, respectively.

There was a consistent pattern of variation when different charge measurement times were employed. This can be most easily seen by looking at the coefficient of variation of the well chamber calibration coefficient and the coefficient of variation of the calculated seed activity for different measurement times. Increasing measurement time generally lowered the coefficient of variation by a factor of two for higher activity seeds and up to a factor of four for low activity seeds. The coefficients of variation for each calibration coefficient and for each seed apparent activity result (For Seed 2 through Seed 6) are shown in Table 2. The only other parameter that had a noticeable effect on the

well chamber calibration coefficient and seed calibration uncertainty was the relative activity of the seed for any particular calibration. Calibration with more recent, higher activity seeds yielded results with less variation. This is also evident from the data in Table 2. Rotation of the seed within the seed holder and flipping the seed end-over-end had no noticeable effect on outcomes. Otherwise, the seed geometry within the well chamber was extremely stable.

Before the accuracy of the calibration results could be analyzed the accuracy and reproducibility of the empirical calibration coefficient of the well chamber used to calibrate each seed was verified. Table 3 shows each chamber calibration coefficient derived from charge accumulation measurements of Seed 1 as well as the reference chamber calibration coefficient from the bi-annual chamber calibration performed May 13, 2014 at the MDACC ADCL. The percent difference between the maximum and minimum chamber calibration coefficient was 1.49%, and the coefficient of variation was 1.14%. Assuming a theoretical chamber calibration coefficient of 0.1802 mCi pA^{-1} (6.67 GBq pA^{-1}) (the chamber factor from the bi-annual ADCL calibration), a two-tailed t-test indicated that the empirical chamber calibration coefficients were not significantly different (95% CI) than the theoretical chamber calibration coefficient. The first empirically derived chamber calibration coefficient of 0.1784 mCi pA^{-1} (6.60 GBq pA^{-1}) was chosen for use in calculations throughout this work.

Table 2. The coefficient of variation is shown for two sets of data. The first set contains the coefficient of variation for the well chamber calibration coefficients based on measurements of Seed 1 on three different days. The second set contains the coefficient of variation for the apparent activities of Seed 2 through Seed 7. The calibration days ranged from 10/24/2014 to 11/9/2014 for the well chamber calibration coefficient and Seed 2 through Seed 6 apparent activity measurements. The Seed 7 apparent activity measurement took place on 11/13/2014. Note that Seed 7 had the highest apparent activity at the time of measurement. Otherwise, apparent activity descends with increasing Seed number. Also, note that the relationship between apparent activity and Seed number is not linear. Seed 2 and Seed 3 (both received from the vendor in July 2014) are very close in apparent activity, as are Seed 5 and Seed 6 (both received from the vendor in April 2014).

		Coefficient of Variation (%)		
	Count Time (s)	Day 1	Day 2	Day 3
Calibration Coefficient CV				
	15	0.28	0.30	0.38
	30	0.30	0.32	0.33
	60	0.19	0.24	0.26
Seed 2 activity CV				
	15	0.69	0.63	0.87
	30	0.31	0.34	0.59
	60	0.31	0.18	0.21
Seed 3 activity CV				
	15	0.60	0.56	0.68
	30	0.41	0.50	0.64
	60	0.23	0.38	0.44
Seed 4 activity CV				
	15	1.11	1.23	1.61
	30	0.79	0.71	0.74
	60	0.58	0.50	0.71
Seed 5 activity CV				
	15	2.49	1.92	2.07
	30	1.22	1.40	1.78
	60	0.67	0.69	0.89
Seed 6 activity CV				
	15	2.37	1.96	3.03
	30	1.25	1.70	1.93
	60	1.10	0.83	1.14
Seed 7 activity CV				
	15	0.26		
	30	0.19		
	60	0.13		

Table 3. The HDR1000 well chamber calibration coefficient was measured on six different days. On the first day, the calibration coefficient was determined by the MDACC ADCL. The other five calibration coefficients were obtained by assaying Seed 1. Seed 1 was measured 20 times for 60 s per trial, and the results were averaged for use in calculating the HDR1000 calibration coefficient in units of mCi pA^{-1}.

Date	I-125 Activity (mCi)	Chamber Factor (mCi pA^{-1})
5/13/2014	ADCL Cal	0.1802±0.0036
10/24/2014	0.130	0.1784±0.0006
10/30/2014	0.121	0.1791±0.0007
11/6/2014	0.112	0.1797±0.0011
11/13/2014	0.103	0.1805±0.0007
11/25/2014	0.090	0.1752±0.0012

HDR1000 Well Chamber ^{125}I Seed Calibration

In a comparison of empirical seed calibration and vendor stated seed calibration, the smallest variation was found with Seed 2 and the largest variation with Seed 6. The Seed 2 activity calibration variation between empirical and vendor ranged from 0.02% to +0.34% difference (calibrated three times), and for Seed 6, the percent difference varied from -1.86% to -2.71%. The empirical-vendor percent difference for all other seeds fell between these values. Seed 1 was calibrated only one time by the ADCL with percent difference -0.84% compared to vendor calibration, while all other seeds were calibrated three times (Seed 7 was only calibrated two times) in the HDR1000 well camber, thus a range of percent difference values are given for Seed 2 through Seed 7. All apparent activity data are shown in Table 4, including the vendor stated calibration (decay corrected). Constancy tests were also performed each day with a ^{133}Ba standard rod source (SS&DR No. CA0406S107S, Isotope Products Laboratory, 24937 Ave Tibbitts, Valencia, CA 91355), the results of which are given in Table 5.

Table 4. Apparent activity measurements (made in this work and by vendor) are shown for each seed along with the percent difference between the experimental measurements and the vendor stated values.

Calibration Date	My HDR100 Calibration (mCi)	Vendor Calibration (mCi)	% Difference
Seed 1			
10/24/14 10:49	0.1303±0.0003	0.1314±0.0003	-0.84%
Seed 2			
10/25/14 19:00	0.0750±0.0004	0.0750±0.0005	0.02%
10/30/14 15:30	0.0711±0.0003	0.0709±0.0005	0.34%
11/6/14 11:15	0.0655±0.0003	0.0654±0.0005	0.10%
Seed 3			
10/25/14 18:00	0.0634±0.0003	0.0640±0.0009	-1.00%
10/30/14 16:45	0.0595±0.0003	0.0604±0.0009	-1.57%
11/6/14 12:35	0.0548±0.0004	0.0558±0.0009	-1.83%
Seed 4			
10/25/14 19:45	0.0317±0.0002	0.0318±0.0006	-0.23%
10/30/14 11:40	0.0294±0.0003	0.0301±0.0006	-2.32%
11/6/14 13:30	0.0274±0.0002	0.0277±0.0006	-1.11%
Seed 5			
10/25/14 19:45	0.0219±0.0002	0.0221±0.0006	-0.75%
10/31/14 12:40	0.0201±0.0003	0.0206±0.0006	-2.67%
11/6/14 14:15	0.0187±0.0002	0.0192±0.0006	-2.81%
Seed 6			
10/25/14 21:30	0.0192±0.0002	0.0196±0.0011	-1.86%
10/31/14 15:40	0.0178±0.0002	0.0183±0.0011	-2.71%
11/6/14 15:50	0.0166±0.0003	0.0171±0.0011	-2.68%
Seed 7			
11/13/14 13:30	0.1785±0.0008	0.1823±0.0008	-2.10%
11/25/14 16:45	0.1588±0.0007	0.1582±0.0008	0.37%
		mean % diff	-1.31%
		Stdev % diff	1.12%
		95% CI lower	-3.51%
		95% CI upper	0.88%

Table 5. Constancy tests were performed on the HDR1000 on each day that ^{125}I seed assays were performed. The average of six 15 s charge accumulations of a ^{133}Ba standard rod source on each day are compared below. All charge accumulation values (HDR1000 measurements) are in units of pC. The percent differences between the initial constancy measurements (10/24/2014) and subsequent measurements are given.

Date	10/24/2014	10/25/2014	10/30/2014	10/31/2014	11/6/2014	11/13/2014	11/25/2014
1	-4.08	-4.16	-4.05	-4.16	-4.26	-4.13	-4.02
2	-4.13	-4.12	-4.02	-4.12	-4.18	-4.05	-4.05
3	-4.06	-4.07	-4.07	-4.07	-4.17	-4.14	-4.03
4	-4.13	-4.05	-4.01	-4.05	-4.17	-4.05	-4.00
5	-4.04	-4.05	-4.08	-4.05	-4.06	-4.11	-3.99
6	-4.06	-4.06	-3.99	-4.06	-3.99	-4.05	-3.98
Mean	-4.08	-4.09	-4.04	-4.09	-4.14	-4.09	-4.01
% Diff		-0.04%	1.18%	-1.20%	-1.31%	1.21%	1.88%

Activity Calibrator Calibration

It was found that exchanging two visibly identical glass vials, two visibly identical sample holders and HDR1000 single seed holders had little to no effect on ^{125}I seed assay results. In most cases the same cal numbers yielded the same apparent activity results. When there was a discrepancy, the cal number only needed to be shifted a step or two (<1% change) in order to get the matching apparent activity, and there was no consistent pattern to this shift.

The results of the tests for assay errors due to inconsistent recreation of the geometry configuration are shown in Table 6. When the glass vial geometry configuration was carefully reproduced, the cal numbers ranged from 206 to 210, and when used to assay Seed 1 (0.1030 mCi (3.81 GBq) at the time of assay for this test), the maximum and minimum results were 0.1037 mCi (3.84 GBq) (0.62 % error) and 0.1023 mCi (3.79 GBq) (-0.66 % error), respectively. (Note that lowering the cal number setting increases the displayed apparent activity value). The percent difference between these minimum and maximum apparent activity values was 1.28 %. When the glass vial geometry configuration was intentionally varied, the cal numbers ranged from 190 to 208, which yielded Seed 1 apparent activity values of 0.1097 mCi (4.06 GBq) (6.54 % error) and 0.1023 mCi (3.79 GBq) (-0.66 % error). The percent difference between these minimum and maximum apparent activity values was 7.00 %. For the HDR1000 single seed holder geometry configuration, careful reproduction of the geometry resulted in cal numbers ranging from 367 to 370. This corresponded to ^{125}I apparent activity values of 0.1033 mCi (3.82 GBq) (0.29 % error) and 0.1026 mCi (3.80 GBq) (-0.35 % error), and

the percent difference between the two values was 0.64%. Intentionally varying the HDR1000 geometry configuration resulted in minimum and maximum cal numbers equal to 362 and 368. The apparent activity displayed with these cal number settings was 0.1046 mCi (3.87 GBq) (1.55 % error) and 0.1026 mCi (3.80 GBq) (0.33 % error), and the percent difference between the two values was 1.87 %.

Table 6. The results of the geometry reproducibility tests for the activity calibrator are given below. Both the percent error in the apparent activity values and the percent difference between the maximum and minimum apparent activity values were reasonably small except for the case of inconsistently reproduced geometry with the glass vial. It is possible for the glass vial and the location of the seed to vary greatly inside the well of the activity calibrator. The HDR1000 holder provided a tight fit within the dipper, and thus the well of the activity calibrator, which led to less variation in seed location. All activity values are in units of mCi.

Glass Vial

Consistent Geometry

	Cal#	Assay Activity	ADCL Cal Activity	% Error
Min	206	0.10364	0.1030	0.62%
Max	210	0.10232	0.1030	-0.66%
% difference between max and min			1.28%	

Inconsistent Geometry

	Cal#	Assay Activity	ADCL Cal Activity	% Error
Min	190	0.10974	0.1030	6.54%
Max	208	0.10232	0.1030	-0.66%
% difference between max and min			7.00%	

HDR1000 Seed Holder

Consistent Geometry

	Cal#	Assay Activity	ADCL Cal Activity	% Error
Min	367	0.1033	0.1030	0.29%
Max	370	0.10264	0.1030	-.035%
% difference between max and min			0.64%	

Inconsistent Geometry

	Cal#	Assay Activity	ADCL Cal Activity	% Error
Min	362	0.1046	0.1030	1.55%
Max	368	0.10266	0.1030	-.033%
% difference between max and min			1.87%	

In determining the appropriate cal number for ^{125}I seeds with the glass vial geometry configuration, the mean cal number for each seed's experimental (or ADCL) calibration, vendor calibration, vendor -12 hr and vendor +12 hr apparent activity were 207, 206, 207 and 204, respectively. The cal numbers ranged, over all, from 196 to 225, or a 13.8 % difference between maximum and minimum, but the percent difference between the maximum and minimum cal number for the experimental (or ADCL) calibration ^{125}I seed apparent activity was smaller at 6.27 %. Variation in cal number for any one seed was generally much smaller. For the experimental (or ADCL) calibration ^{125}I seed apparent activity, the percent difference between maximum and minimum cal number for an individual seed (over five measurement days) ranged from 0.48 % (Seed 5) to 3.81 % (Seed 3). There was no obvious correlation between ^{125}I seed apparent activity and variation in cal number. The full experimental cal number results (minimum, maximum, mean, standard deviation, coefficient of variation, $\pm 1\sigma$ and $\pm 2\sigma$ from the mean) for both geometry configurations are shown in Tables 7a and 7b. For the HDR1000 single seed holder geometry configuration, the mean cal numbers were 369, 368, 369 and 364 (experimental calibration, vendor calibration, vendor -12 hr and vendor +12 hr, respectively) with an overall range of 353 to 393 (10.7 % difference). The percent difference between the maximum and minimum cal number for the experimental (or ADCL) calibration ^{125}I seed apparent activity was 4.59 %, and the percent difference between maximum and minimum cal number for any one individual seed (over five measurement days) ranged from 1.62 % (Seed 1) to 3.78 % (Seed 7). Again there was no correlation between seed activity and cal number variation.

Table 7a. Variation in cal numbers obtained from assaying each ^{125}I seed and adjusting the cal number setting until the correct apparent activity is displayed, for the glass vial geometry configuration. The correct apparent activity was determined via experimental (or ADCL) seed calibration as described earlier, vendor stated activity (from calibration certificate) and vendor stated activity under the assumption that the date could be off by ±12 hr if the exact time of day (hour and minute) is ignored. Note that the mean cal numbers and ±1σ and ±2σ from the mean cal numbers need to be rounded before actual use.

	My Cal	Vendor Cal	-12 hr	+12 hr
Min	201	199	199	196
Max	214	223	225	221
% Difference	6.27%	11.37%	12.26%	11.99%
mean	206.8	205.6	207.1	203.7
stdev	3.1	7.4	7.7	7.5
CV	1.49%	3.61%	3.74%	3.70%
-σ	203.8	198. 2	199.3	196.1
-2σ	200.7	190.8	191.6	188.6
+σ	209.9	213.1	214.8	211.2
+2σ	213.0	220.5	222.6	218.8

Table 7b. Same as Table 7a, except the HDR1000 single seed holder geometry was utilized.

	My Cal	Vendor Cal	-12 hr	+12 hr
Min	362	357	357	353
Max	379	390	393	387
% Difference	4.59%	8.84%	9.60%	9.19%
mean	369.3	367.6	368.5	364.2
stdev	4.6	10. 2	10.0	9.5
CV	1.26%	2.77%	2.71%	2.62%
-σ	364.7	357.4	358.6	354.6
-2σ	360.1	347. 2	348.6	345.1
+σ	374.0	377.7	378.5	373.7
+2σ	378.6	387.9	388.5	383.2

In order to assess the ability of an activity calibrator to accurately assay seeds, 28 cal numbers (some happened to be duplicates) were chosen based on the analysis above. The ^{125}I apparent activity values resulting from seed assays at the mean cal number for each seed calibration group (experimental calibration, vendor calibration, vendor -12 hr, vendor +12 hr) are shown in Table 8a and Table 8b, and the percent error (activity calibrator assay compared to "correct" HDR1000 calibration) for each data point is shown in Table 9a and Table 9b. The mean percent error, standard deviation of the percent error data set and the mean percent error 95 % CI, across all seeds (Seed 1 through Seed 5, Seed 7, Seed 8) are also shown in Table 9a and Table 9b. The mean percent error, standard deviation of the percent error data set and the mean percent error 95 % CI, across the five assays of each individual seed are shown in Table 10. The total uncertainty budget for each ^{125}I apparent activity value obtained from seed assays using the mean cal number is shown in Table 11.

Table 8a. Apparent activity data obtained with the glass vial geometry configuration in the activity calibrator, utilizing the mean cal number settings (207, 206, 207, 204) based on four different initial ^{125}I seed calibrations. The theoretical activity is the seed activity calibrated in the HDR1000 (or ADCL for Seed 1) and decayed to the correct date. The day and Seed # column refers to the assay day (1-5) and the Seed # (1-4, 7, 8).

Day and Seed #	My Cal	Vendor Cal	Vendor -12hr	Vendor +12hr	Theoretical Activity	% difference between my cal and vendor cal
1 DC 1	68.1	68.3	68.1	68.9	67.7	-0.29%
1 DC 2	39.1	39.3	39.1	39.6	39.7	-0.51%
1 DC 3	32.2	32.3	32.2	32.6	32.1	-0.31%
1 DC 4	15.6	15.8	15.6	15.9	15.9	-1.27%
1 DC 7	118.0	118.6	118.0	119.3	118.1	-0.51%
1DC 8	200	201	200	202	200.7	-0.50%
2 DC 1	65.0	65.3	65.0	65.7	64.6	-0.46%
2 DC 2	37.4	37.5	37.4	37.7	37.9	-0.27%
2 DC 3	32.2	32.4	32.2	32.6	31.7	-0.62%
2 DC 4	15.6	15.6	15.6	15.7	15.6	0.00%
2 DC 7	110.6	111.5	110.6	112.0	112.9	-0.81%
2 DC 8	198	198	198	200	198.2	0.00%
3 DC 1	60.3	60.5	60.3	61.1	60.3	-0.33%
3 DC 2	34.9	35.0	34.9	35.2	35.4	-0.29%
3 DC 3	30.1	30.3	30.1	30.4	29.6	-0.66%
3 DC 4	14.6	14.6	14.6	14.7	14.6	0.00%
3 DC 7	103.5	103.9	103.5	104.6	105.4	-0.39%
3 DC 8	184	184	184	186	185.0	0.00%
4 DC 1	60.0	60.1	60.0	60.4	59.5	-0.17%
4 DC 2	34.1	34.2	34.1	34.4	34.9	-0.29%
4 DC 3	29.8	29.9	29.8	30.1	29.2	-0.34%
4 DC 4	14.5	14.5	14.5	14.6	14.4	0.00%
4 DC 7	103.2	103.5	103.2	104.2	104.0	-0.29%
4 DC 8	181	182	181	183	182.5	-0.55%
5 DC 1	59.1	59.2	59.1	59.6	58.9	-0.17%
5 DC 2	33.9	34.0	33.9	34.3	34.5	-0.29%
5 DC 3	29.2	29.3	29.2	29.5	28.9	-0.34%
5 DC 4	14.2	14.3	14.2	14.4	14.2	-0.70%
5 DC 7	101.2	101.7	101.2	102.2	102.9	-0.49%
5 DC 8	180	180	180	181	180.7	0.00%

Table 8b. Apparent activity data obtained with the HDR1000 single seed holder geometry configuration in the activity calibrator, utilizing the mean cal number settings (369, 368, 369, 364) based on four different initial ^{125}I seed calibrations. The theoretical activity is the seed activity calibrated in the HDR1000 (or ADCL for Seed 1) and decayed to the correct date. The day and Seed # column refers to the assay day (1-5) and the Seed # (1-4, 7, 8).

Day and Seed #	My Cal	Vendor Cal	Vendor -12hr	Vendor +12hr	Theoretical Activity	% difference between my cal and vendor cal
1 DC 1	67.6	67.7	67.6	68.2	67.7	-0.15%
1 DC 2	39.5	39.7	39.5	39.9	39.7	-0.51%
1 DC 3	32.1	32.1	32.1	32.3	32.1	0.00%
1 DC 4	15.8	15.8	15.8	15.9	15.9	0.00%
1 DC 7	117.2	117.8	117.2	118.5	118.1	-0.51%
1DC 8	194	194	194	195	200.7	0.00%
2 DC 1	64.6	64.9	64.6	65.2	64.6	-0.46%
2 DC 2	37.3	37.5	37.3	37.7	37.9	-0.53%
2 DC 3	31.6	31.7	31.6	32.0	31.7	-0.32%
2 DC 4	15.8	15.8	15.8	15.9	15.6	0.00%
2 DC 7	112.5	112.8	112.5	113.5	112.9	-0.27%
2 DC 8	194	194	194	195	198.2	0.00%
3 DC 1	60.2	60.4	60.2	60.8	60.3	-0.33%
3 DC 2	34.9	35.0	34.9	35.3	35.3	-0.29%
3 DC 3	29.7	29.8	29.7	29.9	29.6	-0.34%
3 DC 4	14.7	14.7	14.7	14.8	14.6	0.00%
3 DC 7	104.4	104.7	104.4	105.4	105.4	-0.29%
3 DC 8	178	179	178	180	185.0	-0.56%
4 DC 1	59.2	59.4	59.2	59.7	59.5	-0.34%
4 DC 2	34.6	34.8	34.6	34.9	34.9	-0.58%
4 DC 3	29.4	29.6	29.4	29.8	29.2	-0.68%
4 DC 4	14.5	14.5	14.5	14.5	14.4	0.00%
4 DC 7	103.1	103.2	103.1	104.0	104.0	-0.10%
4 DC 8	177	177	177	179	182.5	0.00%
5 DC 1	58.8	58.9	58.8	59.3	58.9	-0.17%
5 DC 2	34.2	34.3	34.2	34.5	34.5	-0.29%
5 DC 3	28.8	29.0	28.8	29.1	28.9	-0.69%
5 DC 4	14.3	14.3	14.3	14.4	14.2	0.00%
5 DC 7	103.2	103.4	103.2	104.2	102.9	-0.19%
5 DC 8	175	175	175	177	180.7	0.00%

Table 9a. Percent error in apparent activity data obtained with the glass vial geometry configuration in the activity calibrator, utilizing the mean cal number settings (207, 206, 207, 204) based on four different initial ^{125}I seed calibrations. The day and Seed # column refers to the assay day (1-5) and the Seed # (1-4, 7, 8).

Day and Seed #	My Cal	Vendor Cal	Vendor -12hr	Vendor +12hr
1 DC 1	0.64	0.93	0.64	1.82
1 DC 2	-1.46	-0.96	-1.46	-0.20
1 DC 3	0.33	0.65	0.33	1.58
1 DC 4	-1.58	-0.32	-1.58	0.31
1 DC 7	-0.07	0.43	-0.07	1.03
1DC 8	-0.36	0.14	-0.36	0.64
2 DC 1	0.55	1.01	0.55	1.63
2 DC 2	-1.30	-1.04	-1.30	-0.51
2 DC 3	1.66	2.29	1.66	2.92
2 DC 4	-0.23	-0.23	-0.23	0.41
2 DC 7	-2.04	-1.24	-2.04	-0.80
2 DC 8	-0.12	-0.12	-0.12	0.89
3 DC 1	-0.03	0.30	-0.03	1.29
3 DC 2	-1.35	-1.07	-1.35	-0.51
3 DC 3	1.82	2.50	1.82	2.84
3 DC 4	0.06	0.06	0.06	0.74
3 DC 7	-1.78	-1.40	-1.78	-0.74
3 DC 8	-0.56	-0.56	-0.56	0.52
4 DC 1	0.80	0.97	0.80	1.48
4 DC 2	-2.31	-2.02	-2.31	-1.45
4 DC 3	2.15	2.49	2.15	3.18
4 DC 4	0.69	0.69	0.69	1.38
4 DC 7	-0.72	-0.43	-0.72	0.24
4 DC 8	-0.83	-0.29	-0.83	0.26
5 DC 1	0.27	0.44	0.27	1.12
5 DC 2	-1.77	-1.48	-1.77	-0.61
5 DC 3	1.20	1.55	1.20	2.24
5 DC 4	-0.35	0.35	-0.35	1.05
5 DC 7	-1.68	-1.20	-1.68	-0.71
5 DC 8	-0.41	-0.41	-0.41	0.14
mean	-0.29	0.07	-0.29	0.74
stdev	1.18	1.17	1.18	1.18
95% CI lower	-2.61	-2.22	-2.61	-1.56
95% CI upper	2.02	2.36	2.02	3.04

Table 9b. Percent error in apparent activity data obtained with the HDR1000 single seed holder geometry configuration in the activity calibrator, utilizing the mean cal number settings (369, 368, 369, 364) based on four different initial ^{125}I seed calibrations. The day and Seed # column refers to the assay day (1-5) and the Seed # (1-4, 7, 8).

Day and Seed #	My Cal	Vendor Cal	Vendor -12hr	Vendor +12hr
1 DC 1	-0.10	0.05	-0.10	0.79
1 DC 2	-0.46	0.05	-0.46	0.55
1 DC 3	0.02	0.02	0.02	0.65
1 DC 4	-0.32	-0.32	-0.32	0.31
1 DC 7	-0.75	-0.24	-0.75	0.35
1DC 8	-3.35	-3.35	-3.35	-2.85
2 DC 1	-0.07	0.39	-0.07	0.86
2 DC 2	-1.57	-1.04	-1.57	-0.51
2 DC 3	-0.23	0.08	-0.23	1.03
2 DC 4	1.05	1.05	1.05	1.69
2 DC 7	-0.35	-0.09	-0.35	0.53
2 DC 8	-2.14	-2.14	-2.14	-1.63
3 DC 1	-0.20	0.13	-0.20	0.79
3 DC 2	-1.35	-1.07	-1.35	-0.22
3 DC 3	0.47	0.81	0.47	1.15
3 DC 4	0.74	0.74	0.74	1.43
3 DC 7	-0.93	-0.64	-0.93	0.02
3 DC 8	-3.80	-3.26	-3.80	-2.72
4 DC 1	-0.54	-0.20	-0.54	0.30
4 DC 2	-0.87	-0.30	-0.87	-0.01
4 DC 3	0.78	1.46	0.78	2.15
4 DC 4	0.69	0.69	0.69	0.69
4 DC 7	-0.82	-0.72	-0.82	0.05
4 DC 8	-3.03	-3.03	-3.03	-1.93
5 DC 1	-0.23	-0.07	-0.23	0.61
5 DC 2	-0.90	-0.61	-0.90	-0.03
5 DC 3	-0.18	0.51	-0.18	0.85
5 DC 4	0.35	0.35	0.35	1.05
5 DC 7	0.26	0.46	0.26	1.23
5 DC 8	-3.18	-3.18	-3.18	-2.07
mean	-0.70	-0.45	-0.70	0.17
stdev	1.27	1.30	1.27	1.25
95% CI lower	-3.19	-3.00	-3.19	-2.27
95% CI upper	1.79	2.10	1.79	2.61

Table 10. Each seed was assayed on five different days per cal number. For the mean cal number, the mean percent error in apparent activity (activity calibrator assay compared to "correct" HDR1000 calibration), standard deviation in the percent error and percent error at the 95 % CI, across the five assays of each individual seed are shown below.

Glass vial seed #	Mean	Standard Deviation	95% CI Lower	95% CI Upper
1	0.45	0.33	-0.20	1.09
2	-1.64	0.41	-2.45	-0.83
3	1.43	0.70	0.06	2.81
4	-0.28	0.83	-1.91	1.34
7	-1.26	0.83	-2.88	0.37
8	-0.46	0.26	-0.97	0.06

Seed Holder seed #	mean	stdv	95% CI Lower	95% CI Upper
1	-0.23	0.19	-0.60	0.14
2	-1.03	0.44	-1.89	-0.17
3	0.17	0.44	-0.69	1.03
4	0.50	0.52	-0.52	1.53
7	-0.52	0.49	-1.47	0.43
8	-3.10	0.61	-4.29	-1.90

Table 11a. Total uncertainty in final apparent activity values with the glass vial geometry configuration and mean calibration number. The uncertainty values are given in both apparent activity (uCi) and coefficient of variation (%).

Glass	My Cal (uCi)	+/- (uCi)	CV (%)	Vendor Cal (uCi)	+/- (uCi)	CV (%)	Vendor -12hr (uCi)	+/- (uCi)	CV (%)	Vendor +12hr (uCi)	+/- (uCi)	CV (%)
1 DC 1	68.1	1.0	1.5	68.3	2.5	3.6	68.1	2.6	3.8	68.9	2.6	3.7
1 DC 2	39.1	0.7	1.7	39.3	1.4	3.7	39.1	1.5	3.8	39.6	1.5	3.8
1 DC 3	32.2	0.5	1.7	32.3	1.2	3.7	32.2	1.2	3.8	32.6	1.2	3.8
1 DC 4	15.6	0.3	2.1	15.8	0.6	3.9	15.6	0.6	4.0	15.9	0.6	4.0
1 DC 7	118.0	1.8	1.6	118.6	4.3	3.6	118.0	4.4	3.8	119.3	4.5	3.7
1DC 8	200	3.1	1.5	201	7.3	3.6	200	7.5	3.8	202	7.5	3.7
2 DC 1	65.0	1.0	1.5	65.3	2.4	3.6	65.0	2.4	3.8	65.7	2.4	3.7
2 DC 2	37.4	0.6	1.7	37.5	1.4	3.7	37.4	1.4	3.8	37.7	1.4	3.8
2 DC 3	32.2	0.5	1.7	32.4	1.2	3.7	32.2	1.2	3.8	32.6	1.2	3.8
2 DC 4	15.6	0.3	2.1	15.6	0.6	3.9	15.6	0.6	4.0	15.7	0.6	4.0
2 DC 7	110.6	1.7	1.6	111.5	4.1	3.6	110.6	4.2	3.8	112.0	4.2	3.7
2 DC 8	198	3.1	1.5	198	7.2	3.6	198	7.4	3.8	200	7.4	3.7
3 DC 1	60.3	0.9	1.5	60.5	2.2	3.6	60.3	2.3	3.8	61.1	2.3	3.7
3 DC 2	34.9	0.6	1.7	35.0	1.3	3.7	34.9	1.3	3.8	35.2	1.3	3.8
3 DC 3	30.1	0.5	1.7	30.3	1.1	3.7	30.1	1.2	3.8	30.4	1.2	3.8
3 DC 4	14.6	0.3	2.1	14.6	0.6	3.9	14.6	0.6	4.0	14.7	0.6	4.0
3 DC 7	103.5	1.6	1.6	103.9	3.8	3.6	103.5	3.9	3.8	104.6	3.9	3.7
3 DC 8	184	2.8	1.5	184	6.7	3.6	184	6.9	3.8	186	6.9	3.7
4 DC 1	60.0	0.9	1.5	60.1	2.2	3.6	60.0	2.3	3.8	60.4	2.2	3.7
4 DC 2	34.1	0.6	1.7	34.2	1.3	3.7	34.1	1.3	3.8	34.4	1.3	3.8
4 DC 3	29.8	0.5	1.7	29.9	1.1	3.7	29.8	1.1	3.8	30.1	1.1	3.8
4 DC 4	14.5	0.3	2.1	14.5	0.6	3.9	14.5	0.6	4.0	14.6	0.6	4.0
4 DC 7	103.2	1.6	1.6	103.5	3.8	3.6	103.2	3.9	3.8	104.2	3.9	3.7
4 DC 8	181	2.8	1.5	182	6.6	3.6	181	6.8	3.8	183	6.8	3.7
5 DC 1	59.1	0.9	1.5	59.2	2.2	3.6	59.1	2.2	3.8	59.6	2.2	3.7
5 DC 2	33.9	0.6	1.7	34.0	1.3	3.7	33.9	1.3	3.8	34.3	1.3	3.8
5 DC 3	29.2	0.5	1.7	29.3	1.1	3.7	29.2	1.1	3.8	29.5	1.1	3.8
5 DC 4	14.2	0.3	2.1	14.3	0.6	3.9	14.2	0.6	4.0	14.4	0.6	4.0
5 DC 7	101.2	1.6	1.6	101.7	3.7	3.6	101.2	3.8	3.8	102.2	3.8	3.7
5 DC 8	180	2.8	1.5	180	6.5	3.6	180	6.8	3.8	181	6.7	3.7

Table 11b. Total uncertainty in final apparent activity values with the HDR1000 single seed holder geometry configuration and mean calibration number. The uncertainty values are given in both apparent activity (uCi) and coefficient of variation (%).

Seed Holder	My Cal (uCi)	+/- (uCi)	CV (%)	Vendor Cal (uCi)	+/- (uCi)	CV (%)	Vendor -12hr (uCi)	+/- (uCi)	CV (%)	Vendor +12hr (uCi)	+/- (uCi)	CV (%)
1 DC 1	67.6	0.9	1.3	67.7	1.9	2.8	67.6	1.8	2.7	68.2	1.8	2.6
1 DC 2	39.5	0.6	1.5	39.7	1.1	2.9	39.5	1.1	2.8	39.9	1.1	2.7
1 DC 3	32.1	0.5	1.5	32.1	0.9	2.9	32.1	0.9	2.8	32.3	0.9	2.7
1 DC 4	15.8	0.3	1.8	15.8	0.5	3.1	15.8	0.5	3.1	15.9	0.5	3.0
1 DC 7	117.2	1.6	1.3	117.8	3.3	2.8	117.2	3.2	2.8	118.5	3.2	2.7
1DC 8	194	2.6	1.3	194	5.4	2.8	194	5.3	2.7	195	5.2	2.7
2 DC 1	64.6	0.9	1.3	64.9	1.8	2.8	64.6	1.8	2.7	65.2	1.7	2.6
2 DC 2	37.3	0.5	1.5	37.5	1.1	2.9	37.3	1.0	2.8	37.7	1.0	2.7
2 DC 3	31.6	0.5	1.5	31.7	0.9	2.9	31.6	0.9	2.8	32.0	0.9	2.7
2 DC 4	15.8	0.3	1.8	15.8	0.5	3.1	15.8	0.5	3.1	15.9	0.5	3.0
2 DC 7	112.5	1.5	1.3	112.8	3.2	2.8	112.5	3.1	2.8	113.5	3.0	2.7
2 DC 8	194	2.6	1.3	194	5.4	2.8	194	5.3	2.7	195	5.2	2.7
3 DC 1	60.2	0.8	1.3	60.4	1.7	2.8	60.2	1.6	2.7	60.8	1.6	2.7
3 DC 2	34.9	0.5	1.5	35.0	1.0	2.9	34.9	1.0	2.8	35.3	1.0	2.7
3 DC 3	29.7	0.4	1.5	29.8	0.9	2.9	29.7	0.8	2.8	29.9	0.8	2.7
3 DC 4	14.7	0.3	1.9	14.7	0.5	3.1	14.7	0.5	3.1	14.8	0.4	3.0
3 DC 7	104.4	1.4	1.4	104.7	2.9	2.8	104.4	2.9	2.8	105.4	2.8	2.7
3 DC 8	178	2.4	1.3	179	5.0	2.8	178	4.9	2.7	180	4.8	2.7
4 DC 1	59.2	0.8	1.3	59.4	1.7	2.8	59.2	1.6	2.7	59.7	1.6	2.7
4 DC 2	34.6	0.5	1.5	34.8	1.0	2.9	34.6	1.0	2.8	34.9	1.0	2.7
4 DC 3	29.4	0.4	1.5	29.6	0.9	2.9	29.4	0.8	2.8	29.8	0.8	2.7
4 DC 4	14.5	0.3	1.9	14.5	0.5	3.2	14.5	0.5	3.1	14.5	0.4	3.0
4 DC 7	103.1	1.4	1.4	103.2	2.9	2.8	103.1	2.8	2.8	104.0	2.8	2.7
4 DC 8	177	2.3	1.3	177	5.0	2.8	177	4.9	2.7	179	4.7	2.7
5 DC 1	58.8	0.8	1.3	58.9	1.6	2.8	58.8	1.6	2.7	59.3	1.6	2.7
5 DC 2	34.2	0.5	1.5	34.3	1.0	2.9	34.2	1.0	2.8	34.5	0.9	2.7
5 DC 3	28.8	0.4	1.5	29.0	0.8	2.9	28.8	0.8	2.8	29.1	0.8	2.7
5 DC 4	14.3	0.3	1.9	14.3	0.5	3.2	14.3	0.4	3.1	14.4	0.4	3.0
5 DC 7	103.2	1.4	1.4	103.4	2.9	2.8	103.2	2.8	2.8	104.2	2.8	2.7
5 DC 8	175	2.3	1.3	175	4.9	2.8	175	4.8	2.7	177	4.7	2.7

Ionization Chamber Survey Meter Calibration and ^{125}I Seed Calibration

The variation in survey meter calibration factor was unacceptably high for each of the seeds that were measured. Only Seed 1 and Seed 7 were measured for purposes of calculating the calibration factor, as none of the other seeds had sufficient apparent activity. Seed 1 was later replaced with Seed 8 during the seed assay portion of the experiment. The calibration factor results from one day of Seed 7 results follow as an example. The survey meter calibration factors derived utilizing the glass vial geometry and Seed 7 at 30 cm seed-to-chamber window distance ranged from 1.04 mR hr^{-1} mCi^{-1} (0.244 µSv hr^{-1} GBq^{-1}) to 1.42 mR hr^{-1} mCi^{-1} (0.334 µSv hr^{-1} GBq^{-1}) based on HDR1000 initial ^{125}I seed calibration and 1.03 mR hr^{-1} mCi^{-1} (0.242 µSv hr^{-1} GBq^{-1}) to 1.40 mR hr^{-1} mCi^{-1} (0.329 µSv hr^{-1} GBq^{-1}) based on vendor initial ^{125}I seed calibration. The percent difference between maximum and minimum calibration factors was 30.9 % and 30.5 %, respectively. This included variation in geometry due to disassembly and reassembly. When the source was moved closer to the detector in 2 mm increments (30 cm to 29.2 cm) without disassembly and reassembly, the percent difference in calibration factors for each set of five incremental movements ranged from 5.35 % to 12.57 %. The percent difference due to rotation of the glass vial ranged from 82.6 % to 102.7 % per set of four 90˚ rotations.

The survey meter calibration factors derived utilizing the HDR1000 seed holder geometry at 30 cm seed-to-chamber window distance ranged from 1.20 mR hr^{-1} mCi^{-1} (0.282 µSv hr^{-1} GBq^{-1}) to 1.38 mR hr^{-1} mCi^{-1} (0.324 µSv hr^{-1} GBq^{-1}) and 1.19 mR hr^{-1} mCi^{-1} (0.280 µSv hr^{-1} GBq^{-1}) to 1.36 mR hr^{-1} mCi^{-1} (0.320 µSv hr^{-1} GBq^{-1}). The percent

difference between maximum and minimum calibration factors was 14.0 % and 13.3 %, respectively. This included variation in geometry due to disassembly and reassembly. When the source was moved closer to the detector in 2 mm increments (30 cm to 29.2 cm) without disassembly and reassembly, the percent difference in calibration factors for each set of five incremental movements ranged from 5.04 % to 14.17 %. The percent difference due to rotation of the HDR1000 single seed holder ranged from 50.28 % to 61.81 % per set of four 90˚ rotations.

The mean calibration factors, minimum and maximum calibration factors, and calibration factors at $\pm 1\sigma$ and $\pm 2\sigma$ from the mean calculated from all calibration factors for both Seed 1 and Seed 7 are given in Table 12a and Table 12b. There are four sets of calibration factors per geometry configuration; one set based on the experimental and ADCL calibrations with no variation in source-to-chamber window distance; one set based on the experimental and ADCL calibrations with variation in source-to-chamber window distance; and the other two sets were the same, except the vendor stated ^{125}I seed calibration was used. Included in Tables 12a and 12b is the percent error of the final Seed 7 and Seed 8 apparent activity measurements. These percent error values varied widely with a minimum and maximum of 2.26 % and 46.40 % for Seed 7 with the glass vial geometry configuration and 2.98 % and 31.48 % for the HDR1000 single seed holder configuration. For Seed 8 the minimum and maximum percent error values were 5.21 % and 42.13 % with the glass vial geometry configuration and 1.16 % and 30.67 % for the HDR1000 single seed holder configuration. The low percent error values did not necessary correlate with the mean calibration factor as would be expected. When the

mean calibration factor was used to obtain an apparent activity value the percent error was as high as 29.69 % with the glass vial geometry configuration and 13.9 % with the HDR1000 single seed holder geometry configuration.

Table 12a. The survey meter calibration factors (mR hr^{-1} mCi^{-1}) (mean calibration factor, ±1σ and ±2σ from the mean calibration factors, minimum and maximum calibration factors) are listed along with the percent error in the apparent activity values derived from the measured exposure rate data (unit conversion with calibration factors). These are for the glass vial geometry configuration. When the correction factor is listed at ~30 cm, it was derived from the set of exposure rate data where the source-to-chamber window distance was varied in 2 mm increments.

	CF (My Cal) 30cm	Seed 7 % Error	Seed 8 % Error
Min	0.7855	6.79%	15.72%
-2σ	0.7776	7.87%	16.90%
-σ	0.9620	12.80%	5.51%
Mean	1.1464	26.83%	20.71%
+σ	1.3309	36.97%	31.70%
+2σ	1.5153	44.64%	40.01%
Max	1.4249	41.13%	36.21%
	CF (My Cal) ~30cm		
Min	0.6982	20.14%	30.19%
-2σ	0.7907	6.09%	14.96%
-σ	0.9782	14.25%	7.08%
Mean	1.1657	28.04%	22.02%
+σ	1.3532	38.01%	32.83%
+2σ	1.5407	45.56%	41.00%
Max	1.5035	44.21%	39.54%
	CF (Vendor Cal) 30cm		
Min	0.8203	2.26%	10.81%
-2σ	0.8107	3.47%	12.12%
-σ	0.9917	15.41%	8.34%
Mean	1.1727	28.47%	22.49%
+σ	1.3536	38.03%	32.85%
+2σ	1.5345	45.34%	40.76%
Max	1.4195	40.91%	35.96%
	CF (Vendor Cal) ~30cm		
Min	0.7291	15.05%	24.67%
-2σ	0.8152	2.90%	11.50%
-σ	1.0041	16.46%	9.47%
Mean	1.1930	29.69%	32.81%
+σ	1.3819	39.30%	34.22%
+2σ	1.5708	46.60%	42.13%
Max	1.5209	44.85%	40.23%

Table 12b. The survey meter calibration factors (mR hr^{-1} mCi^{-1}) (mean calibration factor, ±1σ and ±2σ from the mean calibration factors, minimum and maximum calibration factors) are listed along with the percent error in the apparent activity values derived from the measured exposure rate data (unit conversion with calibration factors). These are for the HDR1000 single seed holder geometry configuration. When the correction factor is listed at ~30 cm, it was derived from the set of exposure rate data where the source-to-chamber window distance was varied.

	CF (My Cal) 30cm	Seed 7 % Error	Seed 8 % Error
Min	0.7855	13.63%	6.09%
-2σ	0.7776	27.42%	18.97%
-σ	0.9620	10.16%	2.86%
Mean	1.1464	2.98%	9.41%
+σ	1.3309	13.32%	19.06%
+2σ	1.5153	21.66%	26.86%
Max	1.4249	16.95%	22.46%
	CF (My Cal) ~30cm		
Min	0.6982	31.48%	22.76%
-2σ	0.7907	20.23%	12.26%
-σ	0.9782	5.86%	1.16%
Mean	1.1657	5.43%	11.71%
+σ	1.3532	14.56%	20.23%
+2σ	1.5407	22.08%	27.25%
Max	1.5035	21.22%	26.44%
	CF (Vendor Cal) 30cm		
Min	0.8203	15.42%	7.76%
-2σ	0.8107	29.44%	20.86%
-σ	0.9917	9.31%	2.06%
Mean	1.1727	5.41%	11.68%
+σ	1.3536	16.63%	22.16%
+2σ	1.5345	25.47%	30.42%
Max	1.4195	19.64%	24.97%
	CF (Vendor Cal) ~30cm		
Min	0.7291	25.92%	17.57%
-2σ	0.8152	21.61%	13.55%
-σ	1.0041	4.89%	2.06%
Mean	1.1930	7.79%	13.90%
+σ	1.3819	17.73%	23.19%
+2σ	1.5708	25.74%	30.67%
Max	1.5209	24.54%	29.55%

CONCLUSIONS AND DISCUSSION

Conclusions

1. The radionuclide activity calibrator can be used to calibrate ^{125}I brachytherapy seeds for use in RSL procedures. The results of this work have shown that the activity calibrator can be calibrated (by determining an accurate calibration number for a specific seed type and vendor) so that ^{125}I seed assays are accurate (percent error <5% when compared to theoretical source strength), precise (small standard deviation), contain relatively small uncertainty (CV = ~3% or less) and are reproducible over time and for seeds of varying apparent activity. For the glass vial geometry configuration, when the percent error in apparent activity values of all seeds are pooled and averaged (considering only activity calibrator assays with the mean cal number), the sample mean percent error was -0.29 %, and the true mean percent error was between -2.61 % and 2.02 % with 95 % confidence for experimental (HDR1000) calibration and -2.22 % and 2.36 % (95 % CI) for vendor calibration (See Table 9a). For the average of individual seed (over five seed assay days) percent error in apparent activity values, the variation in mean value was less than when all seeds are pooled together (See Table 10). For vendor calibration with a ±12 hr offset (still based on mean cal number) the highest percent error for any single data point was 3.18% and the mean percent error was within ±1%. For the HDR1000 single seed holder geometry configuration, the sample mean percent error was -0.70 %, and the true mean percent error was between -3.19 % and 1.79 % with 95 % confidence for experimental (HDR1000) calibration and -3.00 % and 2.10 % (95 % CI) for vendor

calibration, which were both slightly wider than for the glass vial geometry configuration. All of these values fall well within the regulatory limit of 10 % as well as the recommended internal check limit of 5%. For brachytherapy procedures, AAPM Report # 84 gives a dose rate uncertainty analysis, which assumes an uncertainty of at least 3% in source strength (*Rivard et al.* 2004). The total uncertainty in apparent activity (considering only activity calibrator assays with the mean cal number) is comparable for both the glass vial and the HDR1000 single seed holder (See Table 11). For almost every seed assay with the HDR1000 single seed holder, the total uncertainty is actually less than 3%.

2. The initial HDR1000 calibration apparent activity for each seed is compared to vendor stated apparent activity in Table 4. The final experimental calibration (with radionuclide activity calibrator) apparent activity values are given in Table 8. Interestingly, the final percent difference in experimental and vendor calibration data (see last column of Table 8) show considerably less variation than the initial percent difference in HDR1000 calibration and vendor calibration data (see last column of Table 4). Apparently, the measurement and averaging process used to obtain the mean cal number produced nearly identical cal numbers for each set of ^{125}I seed initial calibration values (experimental calibration, vendor stated calibration, and vendor ±12 hr).

Paired t-tests were performed on the eight sets of apparent activity percent difference data (See Table 9). For the glass vial geometry configuration, the four data sets were not statistically different from each other. For the HDR1000 single seed holder

geometry configuration, the difference between the data sets was significant. This was due to the percent error in Seed 8 apparent activity measurements, which were slightly over 3%. Most of the data points for the other seeds were below 1%. Removing this seed from the data resulted in data sets that were no longer statistically different. When comparing data sets between the two geometry configurations, the difference was significant.

3. The ionization chamber survey meter cannot be used to calibrate ^{125}I brachytherapy seeds for use in RSL procedures with the methods investigated in this work. Human error in exposure rate data collection and thus, calibration factor determination, was substantial. Even if geometry reproducibility was perfect (which it certainly is not), the inherent instability in exposure rate readout produces unacceptable variation in data. Even the mean calibration factors produced apparent activity values with percent error greater than 10 % (See Table 12). When source rotation is factored in, the percent error values become considerably larger. Source rotation is inevitable with the glass vial and can lead to calibration factor percent error values greater than 100 %. This is because inside the glass vial, the seed can rotate so that either the end or the horizontal (length or height) side of the seed (or anywhere in between) faces the detector. The radiation field is quite different in these two orientations. In the case of the HDR1000 single seed holder, the seed rotates with the seed length (height) as its axis. In this rotational field, the source is isotropic, yet still rotation caused calibration factor percent error values greater than 60 %. This is due to the physical design of the

HDR1000 single seed holder. There are three thin "pillars" that assure the structural integrity of the seed holder. If one of these pillars is in between the seed and the detector window, the exposure rate at the detector window will drop off significantly.

4. The percent error in the apparent activity measurements made with the activity calibrator decreased with increasing ^{125}I seed activity. This was quite noticeable when assaying all seeds (initial seed vendor calibrations spanning nine months). This relationship was not evident on short time scales. When observing individual seeds (5 measurements over 1-2 months), the percent error data did not correlate strongly with seed activity.

5. In practice, an institution performing RSL procedures should not need to duplicate every step of this thesis work before deploying a general-purpose radionuclide activity calibrator for RSL seed source strength verification. A geometry configuration would need to be selected and tested for reproducibility if the configuration differs from the two configurations presented in this thesis. While it may not be necessary or practical to assay six different seeds, a single seed would not be sufficient. Multiple seeds (from the seed vendor) possessing NIST traceable calibration should be assayed in the radionuclide activity calibrator in order to determine the optimal calibration number (or correction factor if a factory calibration number is utilized). Three is recommended as a minimum number of seeds, and the mean calibration number (or correction factor) from these assays should be used in future RSL seed assays. Ideally, the ^{125}I seed vendor should

provide proof of NIST traceability for the first three calibration seeds that it sends to an institution starting a RSL program. Alternatively, three seeds (from any recent batch) could be sent to an ADCL to receive a NIST traceable calibration.

Summary of Contributions

I have demonstrated that a general-purpose radionuclide activity calibrator can be used for RSL seed calibration by following the steps put forth in this thesis. While all experiments were performed with only IsoAid ^{125}I seeds, it is expected that these procedures will work with seeds from other vendors, although the calibration number may be different. This would obviate the need for a specialized brachytherapy seed calibration system within a clinic that only uses these seeds for RSL procedures. I have also proven the feasibility of two reproducible seed assay geometry configurations. The HDR1000 single seed holder can be purchased separately from the HDR1000 well chamber system, and it is a very good fit with the activity calibrator sample holder used in this work. Geometry reproducibility tests show that it is not possible for the user to introduce significant error through careless reproduction of the HDR1000 single seed holder geometry configuration. On the other hand, the user must be more careful when using the glass vial that the ^{125}I calibration seed is shipped in as part of the activity calibrator seed assay geometry configuration. Geometry reproducibility tests have shown that if the glass vial is placed in the center of the sample holder every time, then reproducibility is achieved, but unacceptable uncertainty can be introduced if the glass vial position varies within the sample holder.

I have provided evidence that the choice of initial ^{125}I apparent activity (in-house HDR1000 versus vendor stated valued) for use in determining the optimal activity calibrator cal number is potentially less crucial than one might expect. The differences between initial ^{125}I apparent activity caused only slight variation in cal number, and in turn, small variation in the results of activity calibrator assays. Thus, even though the half-life of ^{125}I is short enough to justify using exact times (hour and minute), if only the exact day is used, apparent activity verification measurements made with a activity calibrator can still be sufficient for regulatory purposes. Furthermore, a two-tailed t-test shows that the eight sets of percent error in apparent activity data (four per geometry configuration) are not statistically different from each other.

Finally, I have provided evidence that in-house ^{125}I seed apparent activity measurements made with a HDR1000 well chamber are generally within 3 % of apparent activity values given by IsoAid on the vendor calibration certificate (See Table 4). A larger number of ^{125}I seeds would need to be assayed in order to verify this.

Future Research

1. The calibration methodology put forth in the Conclusions section should be developed into a formally written procedure, tested and implemented by qualified medical physicists in institutions currently performing RSL procedures. The written procedure should be as efficient as possible without compromising regulatory

compliance. The methodology given in the Conclusions section recommends that the physicist utilize three NIST traceable seeds, contrary to the eight total seeds used in this thesis work. Future research should aim to verify that three seeds are sufficient to determine the optimal cal number.

2. The relationship between ^{125}I seed activity and the percent error in the apparent activity measurements made with the activity calibrator should be further analyzed. In subsequent experiments, the number of calibration seeds should be increased in order to substantiate the third conclusion made above, and the seeds should be measured more frequently and for a longer overall period of time to determine specific limits on how long after vendor seed calibration the ^{125}I can be assayed in the activity calibrator while keeping the percent error in the measurement reasonable. The second conclusion above should also be further investigated utilizing a greater number of seeds. It would be very convenient for the user if the second conclusion were proven to be true in general. It would also be useful to quantify the limits to the amount of variation in initial ^{125}I seed apparent activity calibration that will still allow for consistent activity calibrator cal number selection and assays with acceptable percent error.

3. Despite the disappointing data obtained with the ionization chamber survey meter, a more refined experiment might yield better results. The glass vial geometry configuration should not be used, and the HDR1000 single seed holder geometry configuration should always be set up in such a way that the support pillars do not

obstruct the radiation field between the source and the detector. Most importantly, the methodology for obtaining survey meter measurement results must be more accurate. This could be achieved by recording the data with the built-in software. An adapter/computer interface cable (RS-232, Fluke Biomedical, 6920 Seaway Blvd, Everett, WA 98203) is used to connect the survey meter to a computer. This software automatically records and stores (in a Microsoft Excel spreadsheet on the host computer) exposure rate measurements at predefined time intervals. Averaging a large number of readings over consistent time intervals could result in improved accuracy and reproducibility.

4. Other radiation detection instruments might be serviceable for ^{125}I seed source strength verification. Specifically, any instrument capable of low-energy gamma spectroscopy should be investigated. NaI detectors, both benchtop and portable could theoretically be placed in a fixed geometry for gamma spectrum data acquisition and analysis. A NaI thyroid bioassay system may already be in place if the institution performing RSL procedures has a nuclear medicine department. Spectroscopy systems based on CdTe crystals have become more common and are excellent for low-energy gamma and x-ray spectroscopy, as well. Success with any of these systems will be highly dependent on reproducibility of a fixed geometry. These systems are also more time intensive (than radionuclide activity calibrator measurements) and require staff that is experience with gamma spectroscopy.

Appendix A

Copy of the Seed 1 calibration certificate from IsoAid.

ISOAID

MDACC L00466
RECEIVED: 9/23/14
BY:

CERTIFICATE OF CALIBRATION
ADVANTAGE I-125

Calibration Number: **CN6240**
Lot Number: L 33581
Customer: MD Anderson Cancer Center
Address: Attn: Suzanne Bennett
1155 Pressler Street
Nuclear Medicine ACB6.1537
Houston, TX 77030

Patient Name: First Patient will be Sept 23, 2
Order Number: 201433581
Order Date: Sep 18, 2014

Ten measurements of the apparent activity of a single ADVANTAGE™ I-125 seed, model number IAI-125A was made using a CAPINTEC, Inc. CRC-15BT. The seed was removed from the well chamber after each measurement and randomly reoriented.

Apparent Activity (mCi)	1	2	3	4	5	6	7	8	9	10
	0.200	0.200	0.200	0.200	0.200	0.200	0.200	0.200	0.201	0.200

The Air KERMA strength (uGy m^2 /hr) is obtained by multiplying the iodine-125 apparent activity (mCi) by 1.27.
This value is obtained from published data on other sources.

Air KERMA Strength (uGy m^2/hr)	1	2	3	4	5	6	7	8	9	10
	0.254	0.254	0.254	0.254	0.254	0.254	0.254	0.254	0.255	0.254

Average Apparent Activity: 0.200 (mCi)
Average Air KERMA Strength: 0.254 (uGy m^2/hr)
Date/Time: Sep 18, 2014 10:46 AM CDT

Cal Seed as of Reference Date:
Average Apparent Activity: 0.189 (mCi)
Average Air KERMA Strength: 0.240 (uGy m^2 /hr)
Reference Date/Time: Sep 23, 2014 09:00 AM CDT

1. This seed was measured in accordance with the new National Institute of Standards and Technology standard for Air KERMA strength (1999).
2. This seed passed a leak test showing less than 5 nCi (185 Bq) of removable iodine-125 activity.
3. The air-kerma strength (uGy m^2 /hr) is obtained by multiplying the apparent activity (mCi) by 1.27. This value is obtained from Table IV of "Dosimery of interstitial brachytherapy sources: Recommendations of the AAPM Radiation Therapy Committee Task Group No. 43", Med. Phys., 22(2) 1995.
4. The half-life of iodine-125 is 59.41 days.

Quality Assurance

22, Sep. 2014
Date

Appendix B

Annual accuracy test for activity calibrator used in this thesis work. The accuracy test was performed by Department of Imaging Physics staff.

Dose Calibrator Annual Test: Accuracy

Location	ACB NM RIA Lab
CAPINTEC Serial No.	157227
Measurement Date	12/17/14

Reference Isotope Information:

Isotope*	Serial No.	Activity [uCi]	Date [m/d/y]	Half-Life		Cal # Setting
Co-57	BM06057E10260109	5620.0	9/23/10	271.7	d	112
Ba-133	BM0633-004-09	258.0	8/29/05	10.5	yr	591
Cs-137	BM0637-012-40	204.0	8/22/05	30	yr	220
Sr90/Y90	12974B	32490.0	3/11/05	28.79	yr	056x10

* source form-factor: Benchmark E-Vials, except for the Sr90/Y90 transfer standard

Accuracy PASS Threshold [%] **5**

Reference Isotope	Expected Activity [uCi]	Measurements of Activity [uCi] #1	#2	#3	Mean [uCi]	Std. Dev. [uCi]	CV [%]	Accuracy [%]	
Co-57	109	108	109	108	108.3	0.6	0.53	-0.5	**PASS**
Ba-133	140	144	143	143	143.3	0.6	0.40	2.7	**PASS**
Cs-137	164	168	168	167	167.7	0.6	0.34	1.9	**PASS**
Sr90/Y90	25681	25600	25600	25600	25600	0.0	0.00	-0.3	**PASS**

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