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⟨821⟩ RADIOACTIVITY

1. INTRODUCTION

Radiopharmaceuticals and radioactive devices require specialized techniques in their production, testing, handling, dispensing, and administration in order to ensure optimal effectiveness and maintain safety for workers, patients, and the public. Hence, all operations involving these articles should be carried out by or under the supervision of personnel who have been appropriately trained in the handling of radioactive materials and appropriate instruments.

The facilities for the production, storage, and use of radioactive drugs and radioactive devices are generally subject to licensing by the U.S. Nuclear Regulatory Commission or Agreement State agency, or similar governmental agency outside the United States. Most radioactive drugs and radioactive devices are subject to other regulations relating to transportation, environmental release, and workplace safety.

USP monographs for radioactive articles include specifications for radionuclide identification and assay for radioactivity. Moreover, radioactivity counting assemblies or radiation detectors are required instruments for the determination of radionuclidic purity and radiochemical purity. The purpose of this general chapter is to provide standards for measurement of radioactivity, including instrument qualification, performance checks, identification of radionuclides and radionuclidic impurities, and assay of radionuclides.

Information regarding radioactivity is described in *Radioactivity—Theory and Practice* ⟨1821⟩, which includes definitions, types of decay, general considerations relating to radioactive decay, counting, radionuclide production, purity, labeling, and instrumentation for detection and measurement of radioactive emissions, as well as a glossary.

2. PERSONNEL TRAINING AND DOCUMENTATION

Personnel training should be completed in accordance with written policies and/or procedures. Documentation of the personnel training should be included in the Quality Assurance Program. The length of time to retain the documentation varies depending on the appropriate

regulatory requirements.

3. QUALIFICATION OF INSTRUMENTS

Qualification of instruments should be completed in accordance with written policies and/or procedures. Documentation of the qualification of instruments should be included in the Quality Assurance Program. The length of time to retain the documentation varies depending on the applicable regulatory requirements.

3.1 Installation Qualification

Installation qualification (IQ) is to be performed upon installation of an instrument and after major repair. There are two categories in an IQ—visual inspection and operating environment. Visual inspection involves a check of the condition of the instrument to determine if it is ready to use. The inspection confirms that all cables are intact, the instrument is intact with no broken pieces/parts, and all components of the equipment are in working order. The operating environment for the device is checked for proper temperature, humidity, and power requirements. The operating environment should also be checked to avoid high background radioactivity. Temperatures are typically 10°–30° C and relative humidity ranges are generally 20%–90%. Shielding may be necessary to ensure that the background radiation has no negative effect on the instrument performance.

3.2 Operational Qualification

Operational qualification (OQ) is a check of operational specifications for the equipment, including equipment set-up, functional testing of subsystems, and proper overall operation. OQ should describe operational procedures for the equipment and is performed after IQ and after major repairs. OQ should include all appropriate tests to show that the instrument is capable of functioning properly. Typical examples of OQ include clock accuracy, high voltage, zero adjust, background response, and contamination check.

3.3 Performance Qualification

Performance qualification (PQ) demonstrates that the equipment is capable of performing tasks required in the operating environment and provides the intended results. PQ should describe the required performance tasks for the equipment and include all appropriate tests to demonstrate that the instrument is performing within its operating parameters. These PQ tests are done following the OQ tests. Additionally, some or all the PQ tests are performed routinely (e.g., daily, quarterly, semiannually, annually) to demonstrate the instruments continual acceptance for use. Typical PQ tests include constancy and relative response, accuracy, reproducibility (precision), system linearity, determination of “quench” curves in liquid scintillation counters, and supplier equivalence.

3.4 Geometry Testing

The purpose of the geometry test is to demonstrate correct readings of the test sample, accounting for differences in the container, volume, or position of the test sample compared to the radioactive calibration standard. Geometry testing should be performed at installation of the dose calibrator and for each type of vial and syringe used to contain the test sample. Testing should include the test sample holder. Corrections factors may be developed as needed.

4. ONGOING PERFORMANCE TESTS OF INSTRUMENTS

Performance and operational tests are completed periodically to ensure the instrument is capable of meeting specified criteria for accurate assays and that no changes have occurred since initial testing. Tests include physical inspection, measurement of system parameters, and operational tests with radioactive calibration sources. These tests should also be completed after repair. Regulatory agencies may require specific tests at a regular frequency. The following sections describe the performance tests using a dose calibrator as an example. Ongoing performance tests for other instruments used for radiation measurements should be designed as appropriate to each instrument, testing the parameters that are pertinent to ensuring the performance of the instrument, considering its application and the level of precision of measurement required. The same principles will apply to other instruments used for radiation measurements.

4.1 Physical Inspections

Ensure that the dose calibrator and associated accessories, such as source holders and well liners, are undamaged and that foreign objects are not present in the chamber. Prior to use, repair or replace any damaged components as required and remove all foreign objects.

4.2 System Parameters

The system electronics should be tested according to the manufacturer's diagnostic testing procedures. The results should meet the acceptance criteria detailed in the manufacturer's manual. These parameters typically include the high voltage on the chamber, the zero adjustment on the electrometer, verification of communication between components of the system, and the accuracy of the system clock.

If the manufacturer's diagnostic procedures are not available, then at a minimum the user should check, record, and trend the chamber high voltage and the measured value for the electrometer zero check. Small changes in the high voltage will identify system malfunctions that might not be apparent with the use of radioactive calibration sources, but will begin impacting higher activity readings. The system clock should be checked and should be accurate within one minute.

4.3 Operational Tests

BACKGROUND AND CONTAMINATION TEST

The purpose of this test is to determine the background radiation level and to ensure the absence of contamination that may affect measurements on the dose calibrator. Background radiation may fluctuate due to movement of sources near the chamber, as well as by

contamination in or near the chamber, the liner, or the source holder. For this reason, this test should be performed with the liner and the source holder in the chamber. All radioactive sources should be well shielded or at a sufficient distance from the chamber. The background radiation level should be determined and recorded at initial installation, and periodically verified. The background should be recorded at least once on each day of use, or more frequently if necessary, using the most common radionuclide setting. It is especially important to verify if the minimum assayed quantity of radioactivity decreases.

CONSTANCY TEST

The purpose of this test is to ensure the constancy of the dose calibrator over time. This test should be performed on each day of use, and completed after the system tests outlined above. Typical radioactive calibration sources used in this test are Cesium–137 or Cobalt–60 contained within a solid matrix. Cobalt–57 might not be suitable because of its nominal half-life of less than one year. The radioactive calibration source is not required to have the same geometry as routine test samples. A single radioactive calibration source is sufficient for this check. The source is placed in the source holder and the reading recorded for the dedicated radionuclide setting, as well as for all other commonly used radionuclide settings. This ensures no drift in response for any setting. Results should be recorded and be within the appropriate range of the decay corrected value recorded during IQ. Control charts or other data representations should be used to identify and document trends.

ACCURACY TEST

The purpose of this test is to demonstrate the stability of the dose calibrator over the energy range used. This test should be performed annually or after the dose calibrator is repaired or moved. If the dose calibrator is used to measure the quantity of multiple radionuclides, two or three different radioactive calibration sources with different energies should be included to cover the expected energy range of the radionuclides. These calibration sources are typically contained in a solid matrix and do not necessarily match the geometry of routine test samples. If the dose calibrator is only used for a single radionuclide, or only for positron emission tomography (PET) radionuclides, a single calibration source may be adequate. The quantity of radioactivity in the calibration source should be greater than 100 μCi (3.7×10^6 Bq). Sources used for this test should be traceable to a National Metrology Institute (NMI). Measurements of the calibration source activity are recorded and the average measured value is compared to the expected value. The measured value should be within the appropriate range of the expected value.

REPRODUCIBILITY TEST

The purpose of this test is to measure the precision of the dose calibrator and should be performed at least annually. The radioactive calibration source should have a half-life such that decay corrections are not required over the period of the test. The quantity of radioactivity in the calibration source should be greater than 100 μCi (3.7×10^6 Bq). An appropriate number of consecutive readings are recorded using the same geometry. Each of the measurements taken should be within an appropriate range of the mean of all the measurements.

LINEARITY TEST

The purpose of this test is to show that the response of the dose calibrator is linear across the range of radioactivity levels to be measured. This is especially critical at high levels of radioactivity where the measured radioactivity may differ from the true radioactivity due to saturation effects, and at low levels of radioactivity due to variations on the background radiation and changes in the source positioning. This test should be performed annually or after the dose calibrator has been repaired or moved.

The test is considered successful if the ratio of the measured radioactivity to the expected activity is within the appropriate range of the expected values. Three techniques may be employed for this test: decay, graded shield, and graded source. Use of graded shields is acceptable once an initial linearity test using the decay method is successfully completed. Refer to the manufacturer's recommendations on the use of the graded shields. The graded source method requires accurate measurements of volume or mass, and is not generally recommended.

Table 1 is an example of ongoing performance checks for dose calibrators.

Table 1. List of Performance Tests

Parameter	Daily[a]	Annually (at a minimum)
Physical inspection	Yes	N/A
System electronics	Yes	N/A
Clock accuracy	Yes	N/A
High voltage	Yes	N/A
Zero adjust	Yes	N/A
Background response/contamination check	Yes	N/A

Parameter	Daily[a]	Annually (at a minimum)
Radioactive calibration source (constancy and relative response)	Yes	N/A
Accuracy	See footnote[b]	Yes
Reproducibility (precision)	See footnote[b]	Yes
System linearity	See footnote[b]	Yes

[a] At the beginning of each day of use.

[b] This is required after repair.

5. IDENTIFICATION OF RADIONUCLIDES

5.1 Half-Life Determination

The half-life is an identifying characteristic of a radionuclide. The half-life is determined by measuring the quantity of radioactivity in the test sample as a function of time. The approximate half-life may be used to confirm the radionuclidic identity. Perform the measurements using an appropriately calibrated instrument, such as a quantitative radioactivity detector, provided the quantity of radioactivity is within the linear range of the instrument throughout the measurements and the geometry of the test sample is not changed during the measurements.

The test sample may be used directly, or diluted and/or dried in a capsule as needed. The test sample is prepared in a manner that avoids losses during handling. If the test sample is a liquid or solution, the sample is held in a closed container. If the test sample is a residue from drying in a capsule, the sample is protected by a cover consisting of a sheet of adhesive cellulose acetate or other material. The quantity of radioactivity in the test sample should be sufficient to allow measurements over the time frame of the test. If necessary, correction for dead-time losses may be applied. The measured half-life should be within the range of the expected half-life as defined in each particular application of this test.

5.2 Gamma-Ray Spectrometry

The gamma-ray emission spectrum may be used to identify and quantify gamma-emitting radionuclides. The detector should be calibrated with a radioactive calibration source traceable to a NMI. The calibration source used to determine the efficiency of the detector should have a sufficient quantity of radioactivity to produce an adequate number of counts for each photopeak used in the calibration. The calibration source and the test sample should be measured with the same geometry and distance from the detector. It is critical that the geometry, including vial type and volume, be the same because these factors affect the amount of incident radiation on the detector. Photopeaks in the test sample should be comparable to those in the calibration source, both in terms of energy and intensity. The presence of unknown peaks or changes in peak abundance is indicative of impurities. Ensure that background radiation levels remain constant during the measurement, as changes may result in unknown peaks. Counting time or shielding should be optimized to achieve the necessary required minimum detectable activity to meet test specifications. It may be necessary to allow the radioactivity in the test sample to decay before it is possible to detect impurities at the required levels. There may also be short-lived impurities present, so an analysis should be completed to identify impurities and their half-lives to ensure the sample is assayed prior to their decay. Positron-emitting radionuclides typically cannot be differentiated because their emitted energy (511 keV) is the same for each radionuclide; thus, gamma-ray spectrometry is not a recommended prerelease test for radionuclidic identity for PET radionuclides. Some positron-emitting radionuclides have characteristic gamma-ray emissions in addition to 511 keV, which may be used for purposes of identification (e.g., Ge-69 and Na-22). Performance tests of the gamma-spectroscopy system should be completed on each day of use to ensure the functionality of the system.

5.3 Beta-Emitter Analysis and Identification

The purpose of the beta-emitter analysis and identification is to determine the maximum energy of the beta particle, which is unique and can be used for identification. Beta-emitting radionuclides can be identified either by evaluation of their spectrum or by measuring their mass attenuation coefficients in a series of absorption foils and constructing an attenuation curve. Performance tests of the beta counting system should be completed on each day of use to ensure the functionality of the system.

5.4 Alpha Spectrometry

The alpha emission spectrum may be used to identify and quantify alpha-emitting radionuclides. Pure alpha emitters present unique challenges due to their low penetration distance and their toxicity, especially if they are volatile compounds that could create airborne radioactivity and therefore internal radiation exposure to the experimenter or operator. Alpha particles can be detected either by the use of proportional counters, scintillation detection using a silver-activated zinc sulfide phosphor, or by the techniques of liquid scintillation counting (LSC). Performance tests of the alpha spectroscopy system should be completed on each day of use to ensure the functionality of the system.

6. ASSAY OF RADIONUCLIDES

6.1 Measurement of Radioactivity Using a Dose Calibrator

Using a holder, the test sample is placed in the chamber of the dose calibrator at a given position. Once the response is stable, the radioactivity reading is taken. Performing measurements on the test sample with the same geometry as the calibration source provides the most accurate results; however, geometry correction factors may be developed and used as necessary. Refer to the manufacturer's recommendations for the maximum radioactivity that can be determined in the dose calibrator.

6.2 Measurement of Radioactivity Using a Solid-State Detector

The test sample is positioned in front of the detector or into the well of a well-type detector. The detector must be adequately shielded and calibrated using a radioactive calibration source traceable to an NMI.

6.3 Measurement of Radioactivity Using Chromatographic Systems

A scintillation detector can be used for dynamic radioactivity measurements (e.g., the eluate of a liquid chromatograph is directed over or through a detector). The quantity of radioactivity in the test sample should provide a count rate that is within the linear range of the detector.

6.4 Measurement of Radioactivity Using a Liquid Scintillation Counter

LSC is the standard laboratory method to quantify radioactivity of particle-emitting radionuclides, mostly beta- and alpha-emitting radionuclides. The sample to be analyzed may require a liquid scintillation fluid (cocktail) depending on the energy of the beta particle. The LSC detection method uses liquid scintillation cocktails to transform emitted radiation into detectable light photons. The sample to be analyzed is placed into a liquid scintillation vial and the cocktail is added in the required amount. While a sample that can be dissolved into the fluid is preferred, other samples can be assayed if the impact on the light output is quantified. The detector should be calibrated using an appropriate radioactive calibration source traceable to an NMI. The absorption of scintillation photons is called quench, and it is necessary to develop a “quench curve” during PQ and additional quench curves may be necessary for different types of samples to correct the counting efficiency. Performance tests of the LSC should be completed on each day of use to ensure the functionality of the system.

GLOSSARY

The following definitions apply to commonly encountered words and phrases when dealing with radioactivity.

Alpha particles (α):
Positively charged particles emitted from nuclei during radioactive decay. Alpha particles are Helium-4 nuclei, consisting of two protons and two neutrons, but no electrons.

Beta particles (β^-):
Negatively charged particles that are emitted from nuclei during radioactive decay. Beta particles are electrons.

Calibration factor:
The coefficient used to convert the measured ionization chamber current to a nominal radioactivity. This term is often referred to as the “calibration coefficient”.

Calibration time:
Arbitrary time and date, if appropriate at which the specified amount of radioactivity is present.

Counting assembly:
Consists of a sensing unit and an electronic scaling device. The sensing unit may be a Geiger-Müller tube, a proportional counter, a scintillation detector in which a photomultiplier tube is employed in conjunction with a scintillator, or a solid-state semiconductor.

Dose calibrator:
A well-type ionization chamber commonly used to assay radiopharmaceuticals. Display units are typically in curies (μCi/mCi/Ci) or becquerels (kBq/MBq/GBq).

Gamma rays (γ-rays):
Electromagnetic radiation emitted from nuclei during radioactive decay. Gamma rays have a wide range of energies. The gamma rays emitted from a given radionuclide are always at the same energy(ies) providing a unique signature that enables the identification of a gamma-emitting radionuclide.

Geiger-Müller counter:
Often referred to as “G-M counter” or “Geiger counter”. An instrument in which a high voltage potential is applied across a volume of inert gas for the purpose of collecting ions produced by a radiation field. The negative electrons are internally multiplied to produce a readily detectable current pulse. Display units are typically counts per minute (cpm) or milliroentgen per hour (mR/hr).

Geometry:
The characteristics of a radioactive source (i.e., container type, container wall thickness, volume, and position of the container in the well chamber) that, along with the physical characteristics of the ionization chamber, affect the magnitude of the calibration coefficient for a specific radionuclide. The principal geometry considerations that may affect the accuracy of a source measurement in a dose calibrator are container configuration, source volume, position of the source in the chamber well, and the radionuclide itself.

[Note—It is customary to compare a standardized preparation and radiopharmaceutical drug or preparation using identical geometry conditions for assay, identification, and other parameters. The validity of the result is critically dependent upon the reproducibility of the spatial relationships of the source to the detector and its surroundings and upon the accuracy of the standardized preparation.]

Ionization chamber:

An instrument in which an electric field is applied across a volume of inert gas for the purpose of collecting ions produced by a radiation field. The positive ions and negative electrons drift along the lines of force of the electric field, and are collected on electrodes, producing an ionization current. The most commonly used form of ionization chambers for measurement of the activities of radiopharmaceuticals is a well-type ionization chamber known as a dose calibrator.

Isobars:

Nuclides with the same mass number (protons + neutrons).

Isomers:

Atoms with the same number of protons and neutrons, but a different nuclear energy configuration. Short-lived radioactive isomers are generally referred to as metastable. Different isomers are different nuclides based on their nuclear energy configurations.

Isotones:

Nuclides with the same number of neutrons and a different number of protons. Isotones are different elements with different atomic masses.

Isotopes:

Nuclides with the same number of protons and a different number of neutrons. Isotopes are the same element with a different atomic mass.

Isotopic carrier (also referred to as carrier)**:**

A stable isotope of the element concerned either present in or added to the radioactive preparation in the same chemical form as the radionuclide.

Liquid scintillation counter (LSC):

An instrument which detects scintillation light from the absorption of radiation energy in a scintillation liquid. This instrument is used primarily for beta-emitting radionuclides that do not also emit gamma photons. For best results, the radioactive sample should be soluble in the scintillation liquid.

Minimum detectable activity:

Smallest quantity of radioactivity that can be detected above the background with a specified level of confidence.

National Metrology Institute (NMI)**:**

A measurement standards body, which is a laboratory of metrology that establishes standards for a country or organization. For example, National Institute of Standards and Technology (NIST) is the NMI for the United States.

Nuclide:

An atom with a specific number of protons and neutrons in a given nuclear energy state.

Positrons (β^+)**:**

Positively charged particles emitted from a nucleus during radioactive decay. Positrons are anti-electrons.

Radioactivity:

(1) The spontaneous transformation of nuclei characterized by the emission of particles or photons. Radioactivity is typically described as atoms undergoing radioactive decay per unit time (or disintegrations per unit time). (2) The quantity of radioactive material, as measured in units of curies (U.S. units) or becquerels (SI units). The quantity of radioactive material may also be referred to as activity.

Radiochemical identity:

The molecular structure of the intended active radiopharmaceutical ingredient, which is present in the radiopharmaceutical preparation.

Radiochemical purity:

The ratio, expressed as a percentage, of the radioactivity of the intended active radiopharmaceutical ingredient to the total radioactivity of all radioactive ingredients and impurities present in the radiopharmaceutical preparation.

Radioisotope:

A radioactive atom, generally used in the context of an isotope of an element.

Radionuclide:

An unstable nuclide that undergoes radioactive decay; a radioactive nucleus. The terms radionuclide and radioisotope are commonly used interchangeably.

Radionuclidic identity:

The intended radionuclide in the radiopharmaceutical preparation.

Radionuclidic purity:

The ratio, expressed as a percentage, of the radioactivity of the intended radionuclide to the total radioactivity of all radionuclides in the radiopharmaceutical preparation.

Radiopharmaceutical (radiopharmaceutical preparation/radioactive drug)**:**

A finished dosage form that contains a radioactive substance in association with one or more other ingredients and that is intended to diagnose, stage a disease, monitor treatment, or provide therapy. A radiopharmaceutical includes any nonradioactive reagent kit or radionuclide generator that is intended to be used in the preparation of any such substance. The terms radiopharmaceutical and radioactive drug are commonly used interchangeably.

Scintillation crystal counter:

An instrument consisting of a crystal scintillator, such as NaI (Tl), with attached photomultiplier tube and associated electronics. Scintillation light produced from the absorption of gamma and X-rays in the crystal is converted to electrons and amplified in the photomultiplier tube. The resultant current pulse may be further analyzed with regard to photon energy. A commonly used form of this instrument that has a hole in the crystal of sufficient size to allow placement of a test tube or similar container is known as a “well counter”.

Semiconductor detector:

An instrument consisting of a semiconductor material, such as silicon or germanium crystals, that detects ionizing radiation through generation of charge carriers (passage of electrons through holes). The current pulse produced by migration of these charge carriers, under the influence of a voltage potential across the material, can be further amplified and analyzed to determine the quantity and energy of the incident radiation.

Solid-state detector:

A crystal-based detector, in contrast to a gas-based detector. Often is used as a synonym for a semiconductor detector.

Strength:

The radioactivity concentration of the radiopharmaceutical at the calibration time. The unit of strength is the amount of radioactivity on a volume basis (e.g., mCi/mL or MBq/mL).

Total radioactivity:

The radioactivity of the radionuclide, expressed per unit (e.g., vial, capsule, ampoule, generator, and others) at the calibration time.

Validation:

Establishment of documented evidence that a method, process, or system meets its intended requirements.

Verification:

Confirmation that an established method, process, or system meets predetermined acceptance criteria.

X-rays:

A type of electromagnetic radiation emitted from the electron orbitals. While they do not arise from the nucleus they are often present immediately following a decay event if there are interactions between the emitted radiation and the orbital electrons.

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