BRIEFING

⟨821⟩ Radioactivity, *USP 38* page 616. This chapter was introduced in its current form in 1975 and has not undergone any major revision since its first publication. Currently, the chapter contains definitions, special considerations, and procedures with respect to the monographs for radiopharmaceuticals (radioactive drugs). The majority of this chapter is informational. USP has launched an initiative to minimize nonprocedural information in general chapters with numbers below 1000. The USP Council of Experts believes that ⟨821⟩ should be revised as part of this initiative. To achieve this objective, several members of the USP Council of Experts jointly published a *Stimuli* article in *PF* 38(4) [July–Aug. 2012], *Revision of General Chapter Radioactivity* ⟨821⟩. The objectives of this *Stimuli* article were threefold: (1) provide background information about the need for the proposed revision, (2) initiate discussion about this topic, and (3) solicit public comments for review and discussion by the relevant Expert Committee and Expert Panel members and USP staff.

The current chapter is divided into two major sections, *General Considerations* and *Identification and Assay of Radionuclides*, both of which contain several subsections with information about aspects of radioactivity. Because of the nature of the information presented in these subsections, these can be moved to the proposed *Radioactivity—Theory and Practice* ⟨1821⟩. The *Terms and Definitions* section is now listed as *Glossary* and has been revised to reflect current practices. The revised chapter will contain procedures and information about instrumentation used in the identification and assay of the radionuclides, along with appropriate information about calibration and maintenance of instrumentation. To make the chapter more useful, we propose to include quantitative requirements such as minimum resolution for the detector, allowed variation for instrument performance, and appropriate interval for performance checks, as well as other useful parameters that can ensure the suitability of the equipment for its intended use. Interested parties are invited to submit their comments to the proposed revisions of the chapter.

Additionally, minor editorial changes have been made to update the chapter to current *USP* style.

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⟨821⟩ RADIOACTIVITY

Change to read:

~~Radioactive pharmaceuticals require specialized techniques in their handling and testing in order that correct results may be obtained and hazards to personnel be~~

minimized. All operations should be carried out or supervised by personnel having had expert training in handling radioactive materials.

The facilities for the production, use, and storage of radioactive pharmaceuticals are generally subject to licensing by the federal Nuclear Regulatory Commission, although in certain cases this authority has been delegated to state agencies. The federal Department of Transportation regulates the conditions of shipment of radioactive materials. State and local agencies often have additional special regulations. Each producer or user must be thoroughly cognizant of the applicable regulations of the federal Food, Drug, and Cosmetic Act, and any additional requirements of the U. S. Public Health Service and of state and local agencies pertaining to the articles concerned.

Definitions, special considerations, and procedures with respect to the Pharmacopeial monographs on radioactive drugs are set forth in this chapter.

GENERAL CONSIDERATIONS

Fundamental Decay Law

The decay of a radioactive source is described by the equation:

$$N_t = N_o e^{-\lambda t}$$

in which N_t is the number of atoms of a radioactive substance at elapsed time t, N_o is the number of those atoms when t = 0, and λ is the transformation or decay constant, which has a characteristic value for each radionuclide. The *half-life*, $T_{1/2}$, is the time interval required for a given activity of a radionuclide to decay to one-half of its initial value, and is related to the decay constant by the equation:

$$T_{1/2} = 0.69315/\lambda$$

The activity of a radioactive source (A) is related to the number of radioactive atoms present by the equation:

$$A = \lambda N$$

from which the number of radioactive atoms at time t can be computed, and hence the mass of the radioactive material can be determined.

The activity of a pure radioactive substance as a function of time can be obtained from the exponential equation or from decay tables, or by graphical means based on the half-life (see *Normalized Decay Chart, Figure 1).*

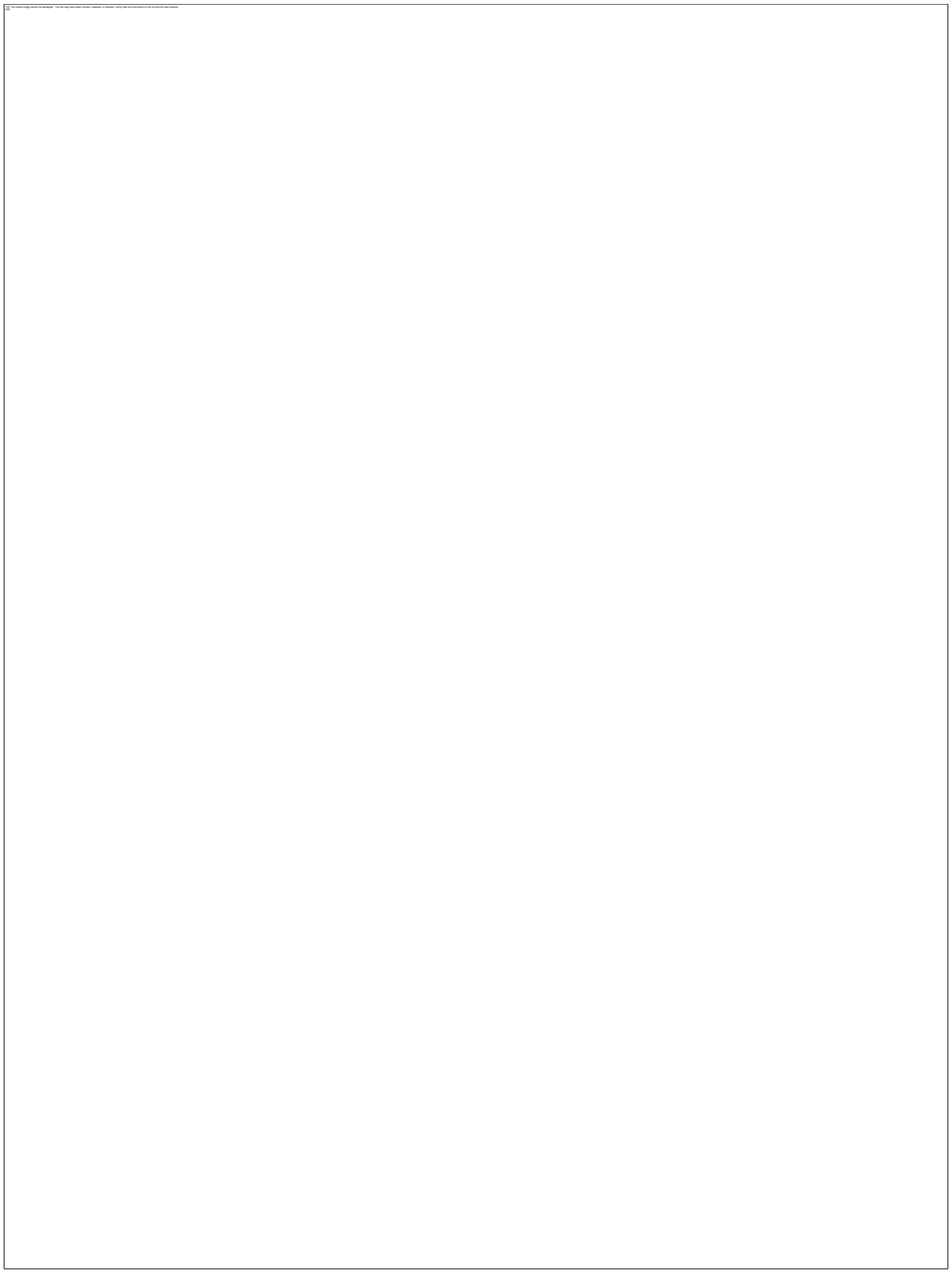


Fig. 1. Normalized Decay Chart.

The activity of a radioactive material is expressed as the number of nuclear transformations per unit time. The fundamental unit of radioactivity, the *curie* (Ci), is defined as 3.700×10^{10} nuclear transformations per second. The *millicurie* (mCi) and *microcurie* (μCi) are commonly used subunits. The "number of nuclear transformations per unit time" is the sum of rates of decay from all competing modes of disintegration of the parent nuclide. Before the activity of any given radionuclide in a measured specimen can be expressed in curies, it is often necessary to know the abundance(s) of the emitted radiation(s) measured.

Geometry

The validity of relative calibration and measurement of radionuclides is dependent upon the reproducibility of the relationship of the source to the detector and its surroundings. Appropriate allowance must be made for source configuration.

Background

Cosmic rays, radioactivity present in the detector and shielding materials, and radiation from nearby radioactive sources not properly shielded from the measuring equipment, all contribute to the background count rate. All radioactivity measurements must be corrected by subtracting the background count rate from the gross count rate in the test specimen.

Statistics of Counting

Since the process of radioactive decay is a random phenomenon, the events being counted form a random sequence in time. Therefore, counting for any finite time can yield only an estimate of the true counting rate. The precision of this estimate, being subject to statistical fluctuations, is dependent upon the number of counts accumulated in a given measurement and can be expressed in terms of the standard deviation σ. An *estimate* for σ is

$$\sqrt{n}$$

where n is the number of counts accumulated in a given measurement. The probability of a single measurement falling within

$$\pm 100/\sqrt{n}\%$$

of the mean of a great many measurements is 0.68. That is, if many measurements of n counts each were to be made, approximately two-thirds of the observations would lie within

$$\pm 100/\sqrt{n}\%$$

of the mean, and the remainder outside.

Because of the statistical nature of radioactive decay, repeated counting of an undisturbed source in a counting assembly will yield count-rate values in accordance with the frequency of a normal distribution. Deviations in these values from the normal distribution conform to the χ^2 test. For this reason, the χ^2 test is frequently applied to determine the performance and correct operation of a counting assembly. In the selection of instruments and conditions for assay of radioactive sources, the figure of merit ε^2/B should be maximized (where ε = counter efficiency = observed count rate/sample disintegration rate, and B = background count rate).

Counting Losses

The minimum time interval that is required for the counter to resolve two consecutive signal pulses is known as the dead time. The dead time varies typically from the order of microseconds for proportional and scintillation counters, to hundreds of microseconds for Geiger-Müller counters. Nuclear events occurring within the dead time of the counter will not be registered. To obtain the corrected count rate, R, from the observed count rate, r, it is necessary to use the formula:

$$R = r/(1 - r_{\tau})$$

in which τ is the dead time. The foregoing correction formula assumes a nonextendable dead time. Thus, for general validity, the value of r_{τ} should not exceed 0.1. The observed count rate, r, refers to the gross specimen count rate and is not to be corrected for background before use in the foregoing equation.

Calibration Standards

Perform all radioactivity assays using measurement systems calibrated with appropriately certified radioactivity standards. Such calibration standards may be purchased either direct from the National Institute of Standards and Technology or from other sources that have established traceability to the National Institute of Standards and Technology through participation in a program of inter-comparative measurements. Where such calibration standards are unavailable, the Pharmacopeia provides the nuclear decay data required for calibration. These data, as well as half-life values, are obtained from the Evaluated Nuclear Structure Data File of the Oak Ridge Nuclear Data Project, and reflect the most recent values at the time of publication.

Carrier

The total mass of radioactive atoms or molecules in any given radioactive source is directly proportional to the activity of the radionuclide for a given half-life, and the amount present in radiopharmaceuticals is usually too small to be measured by ordinary chemical or physical methods. For example, the mass of ^{131}I having an activity of 100 mCi is 8×10^{-7} g. Since such small amounts of material behave chemically in an anomalous manner, carriers in the form of nonradioactive isotopes of the same radionuclide may be added during processing to permit ready handling. In many cases, adsorption can be prevented merely by increasing the hydrogen-ion concentration of the solution. Amounts of such material, however, must be sufficiently small that undesirable physiological effects are not produced. The term “carrier-free” refers only to radioactive preparations in which nonradioactive isotopes of the radionuclide are absent. This implies that radioactive pharmaceuticals produced by means of (n, γ) reactions cannot be considered carrier-free.

The activity per unit volume or weight of a medium or vehicle containing a radionuclide either in the carrier-free state or in the presence of carrier is referred to as the radioactive concentration, whereas the term specific activity is used to express the activity of a radionuclide per gram of its element.

Radiochemical Purity

Radiochemical purity of a radiopharmaceutical preparation refers to the fraction of the stated radionuclide present in the stated chemical form. Radiochemical impurities in

radiopharmaceuticals may result from decomposition and from improper preparative procedures. Radiation causes decomposition of water, a main ingredient of most radiopharmaceuticals, leading to the production of reactive hydrogen atoms and hydroxyl radicals, hydrated electrons, hydrogen, hydrogen ions, and hydrogen peroxide. The last-mentioned is formed in the presence of oxygen radicals, originating from the radiolytic decomposition of dissolved oxygen. Many radiopharmaceuticals show improved stability if oxygen is excluded. Radiation may also affect the radiopharmaceutical itself, giving rise to ions, radicals, and excited states. These species may combine with one another and/or with the active species formed from water. Radiation decomposition may be minimized by the use of chemical agents that act as electron or radical scavengers. Electrons trapped in solids cause discoloration due to formation of F-centers and the darkening of glass containers for radiopharmaceuticals, a situation that typifies the case. The radiochemical purity of radiopharmaceuticals is determined by column, paper, and thin-layer chromatography or other suitable analytical separation techniques as specified in the individual monograph.

Radionuclidic Purity

Radionuclidic purity of a radiopharmaceutical preparation refers to the proportion of radioactivity due to the desired radionuclide in the total radioactivity measured. Radionuclidic purity is important in the estimation of the radiation dose received by the patient when the preparation is administered. Radionuclidic impurities may arise from impurities in the target materials, differences in the values of various competing production cross-sections, and excitation functions at the energy or energies of the bombarding particles during production.

Terms and Definitions

The *date of manufacture* is the date on which the manufacturing cycle for the finished product is completed.

The *date of assay* is the date (and time, if appropriate) when the actual assay for radioactivity is performed.

The *date of calibration* is an arbitrary assigned date and time to which the radioactivity of the product is calculated for the convenience of the user.

The *expiration date* is the date that establishes a limit for the use of the product. The expiration period (i.e., the period of time between the date of manufacture and the expiration date) is based on a knowledge of the radioactive properties of the product and the results of stability studies on the finished dosage form.

Labeling

Individual radiopharmaceutical monographs indicate the expiration date, the calibration date, and the statement, “Caution—Radioactive Material.” The labeling indicates that in making dosage calculations, correction is to be made for radioactive decay, and also indicates the radioactive half-life of the radionuclide. Articles that are Injections comply with the requirements for *Labeling* under *Injections* ⟨1⟩, and those that are Biologics comply with the requirements for *Labeling* under *Biologics* ⟨1041⟩.

IDENTIFICATION AND ASSAY OF RADIONUCLIDES

Instrumentation

IONIZATION CHAMBERS

An ionization chamber is an instrument in which an electric field is applied across a volume of 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. In a properly designed well-type ionization chamber, the ionization current should not be too dependent on the position of the radioactive specimen, and the value of the current per unit activity, known as the calibration factor, is characteristic of each gamma-ray-emitting radionuclide.

The ionization current produced in an ionization chamber is related to the mean energy of the emitted radiation and is proportional to the intensity of the radiation. If standard sources of known disintegration rates are used for efficiency calibration, the ionization chamber may then be used for activity determinations between several microcuries and several hundred millicuries or more. The upper limit of activity that may be measured in an ionization chamber usually is not sharply defined and may be limited by saturation considerations, range of the amplifier, and design of the chamber itself. The data supplied with or obtained from a particular instrument should be reviewed to ascertain the useful ranges of energies and intensities of the device.

Reproducibility within approximately 5% or less can be readily obtained in about 10 seconds, with a deep re-entrant well-type chamber. The most commonly used form of ionization chamber for measurement of the activities of radiopharmaceuticals is known as a dose calibrator.

Although the calibration factor for a radionuclide may be interpolated from an ionization chamber energy-response curve, there are a number of sources of error possible in such a procedure. It is therefore recommended that all ionization chamber calibrations be performed with the use of authentic reference sources of the individual radionuclides, as described hereinafter.

The calibration of a dose calibrator should be maintained by relating the measured response of a standard to that of a long-lived performance standard, such as radium 226 in equilibrium with its daughters. The instrument must be checked daily with the ^{226}Ra or other source to ascertain the stability over a long period of time. This check should include performance standard readings at all radionuclide settings employed. To obtain the activity (A_x) of the radionuclide being measured, use the relationship:

$$A_x = R_x R/R_n$$

in which R_n is the new reading for the radium or other source, R_e is the reading for the same source obtained during the initial calibration procedure, and R is the observed reading for the radionuclide specimen. Obviously, any necessary corrections for radioactive decay of the reference source must first be applied. Use of this procedure should minimize any effects due to drift in the response of the instrument. The recommended activity of the ^{226}Ra or other monitor used in the procedure described above is 75 to 150 µCi. It is recommended also that the reproducibility and/or stability of multirange instruments be checked for all ranges with the use of appropriate standards.

The size and shape of a radioactive source may affect the response of a dose calibrator, and it is often necessary to apply a small correction when measuring a bulky specimen.

SCINTILLATION and SEMICONDUCTOR DETECTORS

When all or part of the energy of beta or gamma radiation is dissipated within scintillators, photons of intensity proportional to the amount of dissipated energy are produced. These pulses are detected by an electron multiplier phototube and converted to electrical pulses, which are subsequently analyzed with a pulse-height analyzer to yield a pulse-height spectrum related to the energy spectrum of the radiation emitted by the source. In general, a beta-particle scintillation pulse-height spectrum approximates the true beta-energy spectrum, provided that the beta-particle source is prepared in such a manner that self-absorption is minimized. Beta-ray spectra may be obtained by using calcium fluoride or anthracene as the scintillator, whereas gamma-ray spectra are usually obtained with a thallium-activated sodium iodide crystal or a large-volume lithium-drifted germanium semiconductor detector. The spectra of charged particles also may be obtained using silicon semiconductor detectors and/or gas proportional counters. Semiconductor detectors are in essence solid-state ionization chambers, but the energy required to create an electron-hole pair or to promote an electron from the valence band to the conduction band in the semiconductor is about one-tenth the energy required for creation of an ion-pair in a gas-filled ionization chamber or proportional counter and is far less than the energy needed to produce a photon in a NaI(Tl) scintillation crystal. In gamma-ray spectrometry, a Ge(Li) detector can yield an energy resolution of 0.33% for 1.33 MeV gamma-rays from ^{60}Co, while a 3- × 3-inch NaI(Tl) crystal can give a value of 5.9% for the same gamma-ray energy. The energy resolution is a measure of the ability to distinguish the presence of two gamma rays closely spaced in energy and is defined by convention as the full width of the photopeak at its half maximum (FWHM), expressed in percentage of the photopeak energy.

Gamma-ray spectra exhibit one or more sharp, characteristic photopeaks, or full-energy peaks, as a result of total absorption in the detector of the full energy of gamma radiations from the source; these photopeaks are useful for identification purposes. Other secondary peaks are observed as a consequence of backscatter, annihilation radiation, coincidence summing, fluorescent X-rays, etc., accompanied by a broad band known as the Compton continuum arising from scattering of the photons in the detector and from surrounding materials. Since the photopeak response varies with gamma-ray energy, calibration of a gamma-ray spectrometer should be achieved with radionuclide standards having well-known gamma-ray energies and emission rates. The shape of the gamma-ray spectrum is dependent upon the shape and size of the detector and the types of shielding materials used.

When confirming the identity of a radionuclide by gamma-ray spectrometry, it is necessary to make a comparison of the specimen spectrum with that of a specimen of known purity of the same radionuclide obtained under *identical instrument parameters and specimen geometry.* Where the radionuclides emit coincident X- or gamma-radiations, the character of the pulse-height distribution often changes quite dramatically because of the summing effect of these coincident radiations in the detector as the efficiency of detection is increased (e.g., by bringing the source closer to the detector). Such an effect is particularly evident in the case of iodine 125. Among the more useful

applications of gamma-ray spectrometry are those for the identification of radionuclides and the determination of radionuclidic impurities.

Where confirmation of the identity of a given radionuclide by means of a direct comparison with the spectrum of a specimen of the same radionuclide of known purity is not possible, the identity of the radionuclide in question must then be established by the following method. Two or more of the following nuclear decay scheme parameters of the radionuclide specimen to be identified shall be measured, and agreement shall be within ±10%: (1) half-life, (2) energy of each gamma- or X-ray emitted, (3) the abundance of each emission, and (4) E_{max} for those radionuclides that decay with beta-particle emissions. Such measurements are to be performed as directed in the *Identification* and *Assay* sections of this chapter. Agreement of two or more of the measured parameters with the corresponding published nuclear decay scheme data constitutes confirmation of the identity of the radionuclide.

LIQUID-SCINTILLATION COUNTERS

Alpha- and beta-emitting radionuclides may be assayed with the use of a liquid-scintillation detector system. In the liquid scintillator, the radiation energy is ultimately converted into light quanta that are usually detected by two multiplier phototubes so arranged as to count only coincidence radiation. The liquid scintillator is a solution consisting of a solvent, primary and secondary solutes, and additives. The charged particle dissipates its energy in the solvent, and a fraction of this energy is converted into fluorescence in the primary solute. The function of the secondary solute is to shift the fluorescence radiation to longer wavelengths that are more efficiently detected by the multiplier phototubes. Frequently used solvents are toluene and *p*-xylene; primary solutes are 2,5-diphenyloxazole (PPO) and 2-(4′-*tert*-butylphenyl)-5-(4-biphenylyl)-1,3,4-oxadiazole (butyl-PBD); and secondary solutes are 2,2′-*p*-phenylenebis[4-methyl-5-phenyloxazole] (dimethyl-POPOP) and *p*-bis(*o*-methylstrylyl)benzene (bis-MSB). As a means of attaining compatibility and miscibility with aqueous specimens to be assayed, many additives, such as surfactants and solubilizing agents, are also incorporated into the scintillator. For an accurate determination of radioactivity of the specimen, care must be exercised to prepare a specimen that is truly homogeneous. The presence of impurities or color in solution causes a decrease in photon output of the scintillator; such a decrease is known as quenching. Accurate radioactivity measurement requires correcting for count-rate loss due to quenching.

The disintegration rate of a beta-particle source may be determined by a procedure in which the integral count rate of the specimen is measured as a function of the pulse-height discriminator bias, and the emission rate is then obtained by extrapolation to zero bias. Energetic alpha-particle emitters may be similarly measured by this method.

Identification

A radionuclide can be identified by its mode of decay, its half-life, and the energies of its nuclear emissions.

The radioactive half-life is readily determined by successive counting of a given source of the radionuclide over a period of time that is long compared to its half-life. The response of the counting assembly when employed for the decay measurement of long-lived radionuclides should be monitored with an even longer-lived reference source to assess and compensate for errors arising from electronic drift. In the case of short-lived

radionuclides, when the counting period constitutes a significant fraction of the half-life of the radionuclide, the recorded count rate must be corrected to the time when the count is initiated, as follows:

$$R_t = r\lambda t/(1 - e^{-\lambda t})$$

in which R_t is the count rate at the beginning of a counting period, r is the count rate observed over the entire counting period, t is the duration of the counting period, λ is the decay constant of the radionuclide, and e is the base of the natural logarithm. When t is small compared to the half-life of the radionuclide under study so that $\lambda t < 0.05$, then $(1 - e^{-\lambda t})$ approaches λt, and no such correction is necessary.

The energy of nuclear emissions is often determined by the maximum range of penetration of the radiation in matter (in the case of alpha- and beta-particles) and by the full-energy peak or photopeak in the gamma-ray spectrum (in the case of X- and gamma-rays). Since beta-particles are emitted with a continuous energy spectrum, the maximum beta-energy, E_{max}, is a unique index for each beta-emitting radionuclide. In addition to the maximum range and energy spectrum of the beta-particles, the absorption coefficient, when obtained under reproducible counting conditions, can serve as a reliable index for identification of a beta-emitter. Fortuitously, beta-particles are absorbed in matter in an approximately exponential manner, and a plot of the logarithm of the beta-particle count rate as a function of the absorber thickness is known as the absorption curve. The initial portion of the absorption curve shows linearity from which the absorption coefficient can be obtained. The maximum range is determined by the use of absorbers of varying thickness, and the energy spectrum is measured by beta-ray scintillation spectrometry.

The absorption of gamma-rays in matter is strictly exponential, but the half-value layers of attenuation have not been very useful for the purpose of radionuclide characterization. Gamma-rays from each isomeric transition are mono-energetic; their energy can be directly measured by gamma-ray spectrometry. Because of their high energy resolution, solid-state detectors [Ge(Li)] are vastly superior to scintillation detectors [NaI(Tl)] in gamma-ray spectrometry.

The activities of radiopharmaceutical solutions are frequently in the range of millicuries per mL. Such solutions usually must be extensively diluted before they can be accurately assayed. The diluent should be compatible with the radiopharmaceutical with respect to factors such as pH and redox potentials, so that no hydrolysis or change in oxidation state occurs upon dilution, which could lead to adsorption and separation of the radionuclide from solution.

BETA-EMITTING RADIONUCLIDES

Mass Absorption Coefficient Procedure—Deposit and dry an aliquot of the radioactive phosphorus 32 solution on a thin plastic film to minimize backscattering, and place it under a suitable counter. Determine the counting rates successively, using not less than six different "thicknesses" of aluminum each between 20 and 50 mg/cm^2 and a single absorber thicker than 800 mg/cm^2, which is used to measure the background. (The absorbers are inserted between the test specimen and the counter but are placed nearer the counter window to minimize scattering.) Net beta-particle count rates are obtained after subtraction of the count rate found with the absorber having a thickness of 800 mg/cm^2 or greater. Plot the logarithm of the net beta-particle count rate as a

function of the total absorber "thickness." The total absorber "thickness" is the "thickness" of the aluminum absorbers plus the "thickness" of the counter window (as stated by the manufacturer) plus the air-equivalent "thickness" (the distance in centimeters of the specimen from the counter window multiplied by 1.205 mg/cm^3 at 20° and 76 cm of mercury), all expressed in mg/cm^2. An approximately straight line results.

Choose two total absorber "thicknesses" that differ by 20 mg/cm^2 or more and that fall on the linear plot, and calculate the mass absorption coefficient, μ, by the equation:

$$\mu = 1/(t_2 - t_1) \cdot \ln (N_{t1}/N_{t2}) = (2.303/(t_2 - t_1)) \times (\log N_{t1} - \log N_{t2})$$

in which t_1 and t_2 represent the total absorber "thicknesses," in mg/cm^2, t_2 being the thicker absorber, and Nt_1 and Nt_2 being the net beta-particle rates with the t_1 and t_2 absorbers, respectively.

For characterization of the radionuclide, the mass absorption coefficient should be within ±5% of the value found for a pure specimen of the same radionuclide when determined under identical counting conditions and geometry.

Other Methods of Identification—Other methods for determining the identity of a beta emitter also rely upon the determination of E_{max}. This may be accomplished in several ways. For example, (1) utilization of the range energy relationships of beta particles in an absorber, or (2) determination of E_{max} from a beta-particle spectrum obtained on an energy-calibrated beta-spectrometer using a thin source of the radionuclide (see *Scintillation and Semiconductor Detectors* in this chapter).

GAMMA-EMITTING RADIONUCLIDES

The gamma-ray spectrum of a radionuclide is a valuable tool for the qualitative identification of gamma-ray emitting radionuclides. The full-energy peak, or the photopeak, is identified with the gamma-ray transition energy that is given in the decay scheme of the radionuclide.

In determining radionuclidic identity and purity, the gamma-ray spectrum of a radioactive substance is obtained with either a NaI(Tl) crystal or a semiconductor Ge(Li) detector. The latter has an energy resolution more than an order of magnitude better than the former and is highly preferred for analytical purposes. The spectrum obtained shall be identical in shape to that of a specimen of the pure radionuclide, measured with the same detection system and in the same geometry. The gamma-ray spectrum of the radiopharmaceutical shall contain only photopeaks identifiable with the gamma-ray transition energies found in the decay scheme of the same radionuclide. For low geometrical efficiencies, the areas under the photopeaks, after correction for the measured detector efficiency, shall be proportional to the abundances or emission rates of the respective gamma-rays in the radionuclide.

RADIONUCLIDIC IMPURITIES

Because they are extremely toxic, alpha-emitting nuclides must be strictly limited in radiopharmaceutical preparations. Procedures for identifying beta- and gamma-active radionuclides as given in the foregoing text are applicable to the detection of gamma and usually beta contaminants.

The gross alpha-particle activity in radiopharmaceutical preparations can be measured by the use of a windowless proportional counter or a scintillation detector employing a silver-activated zinc-sulfide phosphor or by the techniques of liquid-scintillation counting.

The heavy ionization caused by alpha particles allows the measurement of alpha-emitting radionuclides in the presence of large quantities of beta- and gamma-active nuclides by the use of appropriate techniques for discriminating the amplitudes of signal pulses. In proportional counting, the operating voltage region for counting alpha particles, referred to as the "alpha plateau," is considerably lower than the "beta plateau" for counting beta and gamma radiations. Typical "alpha plateau" and "beta plateau" voltage settings with P-10 counting gas are 900 to 1300 and 1600 to 2000 volts, respectively.

When silver-activated zinc-sulfide phosphor is employed for alpha-particle detection, the alpha particles can be distinguished from other interfering radiation by pulse-height discrimination. Care must be exercised to minimize self-absorption at the source whenever specimens are prepared for alpha-particle counting.

Assay

BETA-EMITTING RADIONUCLIDES

Procedure—The disintegration rate (A) of a beta-particle-emitting specimen is obtained by counting a quantitatively deposited aliquot in a fixed geometry according to the formula:

$$A = R/(\varepsilon \times f_r \times f_b \times f_s)$$

in which ε is the counting efficiency of the counter; f_r is the correction factor for counter dead time; f_b is the correction factor for backscatter; and f_s is the correction factor for self-absorption. The count rate for zero absorber is obtained by extrapolation of the initial linear portion of the absorption curve to zero absorber "thickness," taking into consideration the mg/cm^2 "thickness" of specimen coverings, counter window, and the intervening air space between specimen and the counter window. The counter efficiency, ε, is determined by use of a long-lived secondary standard with similar spectral characteristics. RaD + E has frequently been used for efficiency calibration of counters for phosphorus 32. By the use of identical measurement conditions for the specimen and the standard (and extrapolation to zero absorber), the ratio of the values of f_r, f_b, and f_s for the standard and the specimen approaches unity.

The previous relationship is valid also when the counter has been calibrated with a standard of the radionuclide to be assayed. In this case, however, the extrapolations to zero absorber "thickness" for the specimen and standard are not required, as the two absorption corrections cancel for a given geometry.

Another useful and frequently employed method for the determination of the disintegration rate of beta-emitting radionuclides is liquid-scintillation counting, which also utilizes an extrapolation of the specimen count rate to zero pulse-height discriminator bias.

GAMMA-EMITTING RADIONUCLIDES

For the assay of gamma-emitting radionuclides, three methods are provided. The selection of the preferred method is dictated by the availability of a calibration standard of the radionuclide to be assayed and the radionuclidic purity of the article itself.

Direct comparison with a calibration standard is required if a calibration standard of the radionuclide to be assayed is available and if the upper limit of conceivable error in the activity determination arising from the presence of radionuclidic impurities has been

determined to be less than 3%. If the required calibration standard is not routinely available, as would probably be the case for a short-lived radionuclide, but was available at some time prior to the performance of the assay for determination of efficiency of the counting system for the radionuclide to be assayed, use a calibrated counting system, provided the radionuclidic impurity content of the specimen meets the requirements stated for the direct comparison method. If the requirements for either of the first two methods cannot be met, use the method for determination of activity from a calibration curve.

With the exception of the first method, the counting systems used are monitored for stability. This requirement is met by daily checks with a long-lived performance check source and weekly checks with at least three sources covering a broad range of gamma-ray emission energies (e.g., ^{57}Co, ^{137}Cs, and ^{60}Co). If a discrepancy for any of the aforementioned measurements is found, either completely recalibrate or repair and recalibrate the system prior to further use.

Assay by Direct Comparison with a Calibration Standard—An energy selective measurement system (e.g., pulse-height analyzer) is not required for this procedure. Use either an ionization chamber or an integral counting system with a NaI(Tl) detector. A consistently reproducible geometrical factor from specimen to specimen is essential for accurate results. With proper precautions, the accuracy of this method approaches the accuracy with which the disintegration rate of the calibration standard is known.

Determine the counting rate of the detector system for a calibration standard of the radionuclide to be assayed (e.g., active enough to give good measurement statistics in a reasonable time, but not so active as to cause serious dead-time problems), selecting such a standard as to provide optimum accuracy with the particular assembly used. Place an accurately measured aliquot of the unknown assay specimen (diluted, if necessary) in a container identical to that used for the standard, and measure this specimen at approximately the same time and under the same geometrical conditions as for the standard. If the elapsed time between the measurements of the calibration standard and the specimen exceeds 12 hours, check the stability of the measurement system within 8 hours of the specimen measurement time with a long-lived performance check source. Record the system response with respect to the same check source at the time of calibration, and if subsequent checks exceed the original recorded response by more than ±3%, recalibration is required. Correct both activity determinations for background, and calculate the activity, in µCi per mL, by the formula:

$$SD(g/b)$$

in which S is the µCi strength of the standard, D is the dilution factor, and g and b are the measured values of counting rate for the specimen and the standard, respectively.

Assay with a Calibrated Integral Counting System—The procedure and precautions given for the preceding direct-comparison method apply, except that the efficiency of the detector system is determined and recorded for each radionuclide to be assayed, rather than simply recording the counting rate of the standard. Thus, the efficiency for a given radionuclide, x, is determined by $\varepsilon_x = b_x/s_x$, in which b_x is the counting rate, corrected for background and dead-time, for the calibration standard of the radionuclide, x, and s_x is the corresponding activity of the certified calibration standard in nuclear

transformations per second. For subsequent specimen assays, the activity is given by the formula:

$$A_x = Dg_x/\varepsilon_x$$

in which D is the dilution factor, g_x is the specimen counting rate (corrected for background and dead-time), and ε_x is the corresponding efficiency for the radionuclide.

Determination of Activity from a Calibration Curve—Versatility in absolute gamma-ray intensity measurements can be achieved by employing multi-channel pulse-height analysis. The photopeak efficiency of a detector system can be determined as a function of gamma-ray energy by means of a series of gamma-ray emission rate standard specimens, and the gamma-ray emission rate of any radionuclide for which no standard is available can be determined by interpolation from this efficiency curve. However, exercise care to ensure that the efficiency curve for the detector system is adequately defined over the entire region of interest by using a sufficient number of calibration points along the photopeak-energy axis.

Selection of a Counting Assembly—A gamma-ray spectrometer is used for the identification of radionuclides that emit X-rays or gamma rays in their decay. Requirements for an assembly suitable for identification and assay of the radionuclides used in radiopharmaceuticals are that (a) the resolution of the detector based on the 662-keV photopeak of ^{137}Cs-^{137m}Ba must be 8.0% or better, (b) the detector must be equipped with a specimen holder designed to facilitate exact duplication of counting geometry, and (c) the pulse-height analyzer must have enough channels to delineate clearly the photopeak being observed.

Procedure—Minimal requirements for the maintenance of instrument calibrations shall consist of weekly performance checks with a suitable reference source and a complete recalibration semi-annually. Should the weekly performance check deviate from the value determined at the time of calibration by more than 4.0%, a complete recalibration of the instrument is required at that time.

This method involves three basic steps, namely photopeak integration, determination of the photopeak efficiency curve, and calculation of the activity of the specimen.

PHOTOPEAK INTEGRATION—The method for the determination of the required photopeak area utilizes a Gaussian approximation for fitting the photopeak. A fixed fraction of the total number of photopeak counts can be obtained by taking the peak width, a, at some fraction of the maximum, where the shape has been experimentally found to be very close to Gaussian, and multiplying by the counting rate of the peak channel, P, after correction for any Compton and background contributions to the peak channel count rate. This background usually can be adequately determined by linear interpolation. This is illustrated in *Figure 2.*

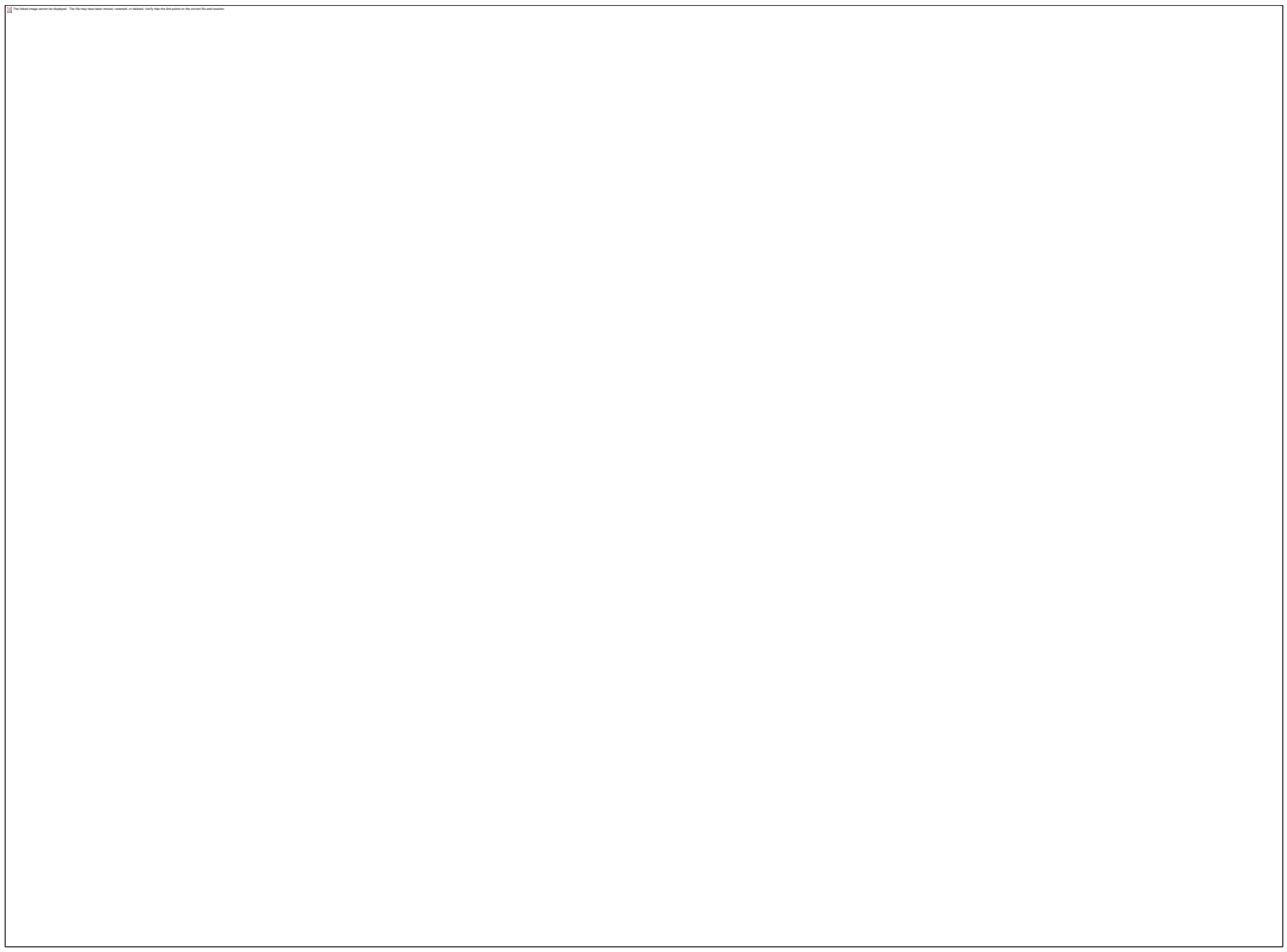
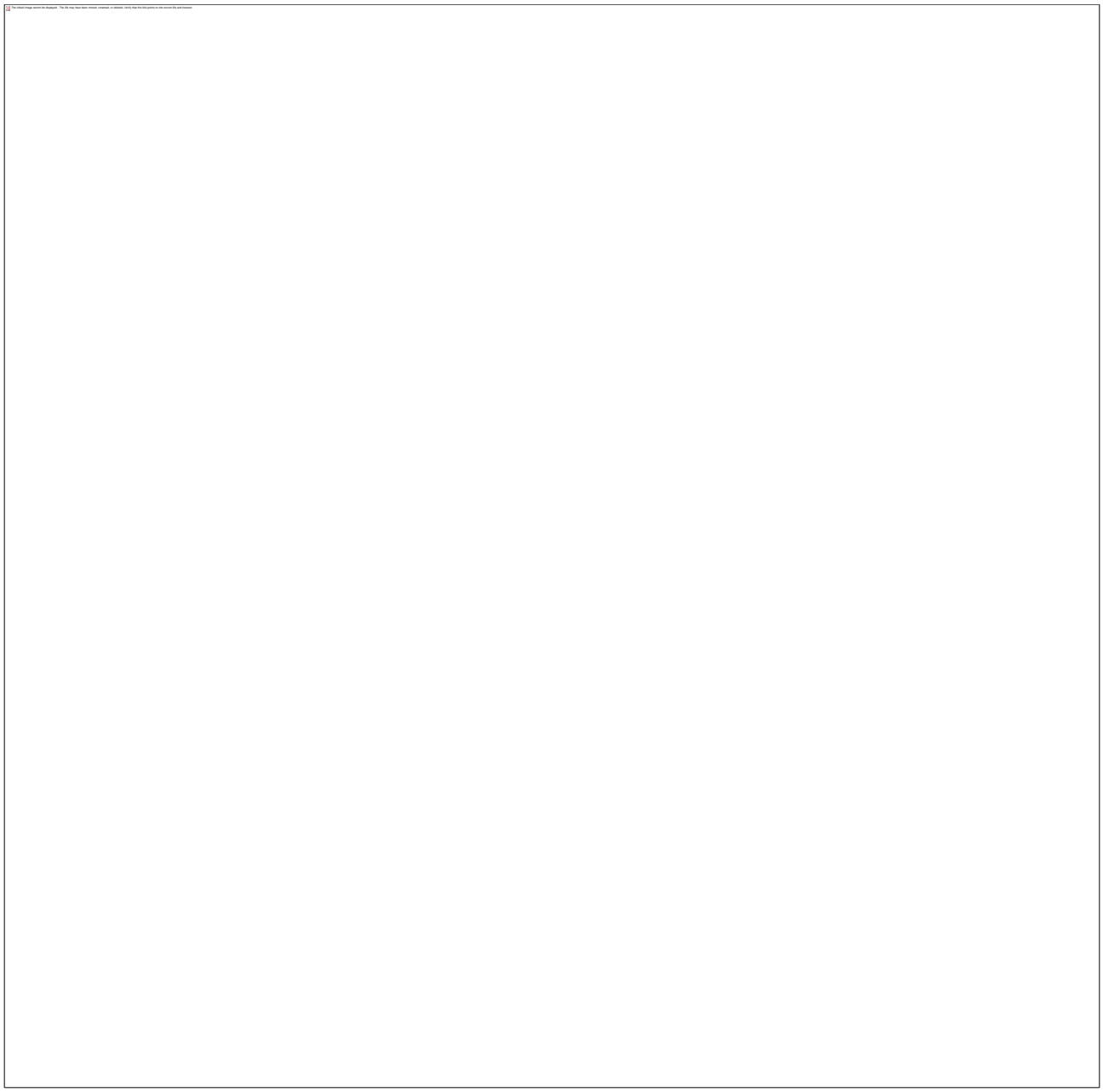


Fig. 2. Typical Gamma-ray Spectrum Showing the Selection of the Peak-Channel Counting Rate, *P*, after the Correction for Compton and Background Contributions.

The photopeak-curve shape is closest to a straight line at 0.606P, and the contribution of the fractional channels to a can be accurately estimated by interpolation. Calculate a by the equation:

$$a = D' - D + [(d - 0.606P)/(d - c)] + [(d' - 0.606P)/(d' - c')]$$

in which c and d and also c′ and d′ are the single *channel counting* rates on either side of 0.606P, and D and D′ are the channel *numbers* (locations) of d and d′, respectively. The location of the required variables on the photopeak is illustrated in *Figure 3*.



From the known values for the counting rate in the peak channel of the photopeak, P, and the width of the peak at 0.606P, a, a calibrated fraction of the photopeak area is then obtained from the product, (aP).

To summarize the procedures involved in obtaining a calibrated fraction of a photopeak area using this method, the necessary steps or calculations are presented below in a stepwise manner:

(1) Subtract any Compton and background contributions from the photopeak to be measured.

(2) Determine the counting rate of the peak channel (maximum channel counting rate after subtracting Compton and background), P.

(3) Multiply P by 0.606, and locate the horizontal line corresponding to the peak width, a.

(4) Obtain the peak width, a, by inserting the values of variables (obtained as shown in the preceding figure) into the equation defining a.

(5) The desired calibrated fraction of the peak area is then equal to the product of a times P or F = aP, where F is a fractional area of the peak proportional to the emission rate of the source.

This method provides a quick and accurate means of determining the gamma-ray emission rate of sources while avoiding, to a large extent, subjective estimates of the detailed shape of the tails of the peaks. The error due to using the maximum channel counting rate, rather than the theoretical maximum or peak channel rate, is of the order of 1.0% if a is 6 or greater.

PHOTOPEAK EFFICIENCY CALIBRATION — Radionuclides such as those listed in the accompanying table together with some of their nuclear decay data are available as certified reference standards.* A sufficient number of radioactive standard reference sources should be selected in order to obtain the calibration curve over the desired range. Where possible, standard sources of those radionuclides that are to be assayed should be included.

Nuclear Properties of Selected Calibration Standards[1,2]

Principal Photon Emissions	Energy (ke V)	Photons per 100 Disintegrations
^{133}Ba ($T_{1/2}$ = 10.5 years)		
$K_{\alpha 1}$	30.97	63.4
$K_{\alpha 2}$	30.62	34.2
K_{β}	35.0	22.8
γ_1	53.15	2.14
γ_2	79.62	2.55
γ_3	80.99	33.0
γ_6	276.39	6.9
γ_7	302.83	17.8
γ_8	356.0	60.0
γ_9	383.85	8.7
^{137}Cs–^{137m}Ba ($T_{1/2}$ = 30.17 years)		
$K_{\alpha 1}$	32.19	3.82
$K_{\alpha 2}$	31.82	2.07
K_{β}	36.4	1.39
Weighted Mean[4]	(32.9)	(7.28)
γ_1	661.6	89.98

Principal Photon Emissions	Energy (ke V)	Photons per 100 Disintegrations
^{22}Na ($T_{1/2}$ = 2.60 years)		
hν	511	179.80[5]
γ_1	1274.54	99.94
^{60}Co($T_{1/2}$ = 5.27 years)		
γ_1	1173.2[6]	100.0
γ_2	1332.5[6]	100.0
^{57}Co($T_{1/2}$ = 270.9 days)		
ΣX_k	7.0	56.0
γ_1	14.4	9.5
γ_2	122.06	85.51
γ_3	136.47	10.60
Weighted Mean ($\gamma_2 + \gamma_3$)[4]	(125.0)	(96.11)
^{54}Mn ($T_{1/2}$ = 312.7 days)		
ΣX_k	6.0	25.0
γ_1	834.83	99.98
^{109}Cd–^{109}Ag($T_{1/2}$ = 464 days)		
$K_{\alpha 1}$	22.16	35.3
$K_{\alpha 2}$	21.99	18.6
K_β	24.9	11.4
Weighted Mean[4]		63.5
γ_1	88.0	3.72
^{129}I($T_{1/2}$ = 1.57 × 10^7 years)		
$K_{\alpha 1}$[3]	29.78	37.0
$K_{\alpha 2}$	29.46	20.0
K_β	13.2	37.0
γ_1	39.58	7.52
Weighted Mean[4]	(31.3)	(77.80)

[1] In measurements for gamma- (or X-)ray assay purposes, fluorescent radiation from lead shielding (specifically, lead K X-rays ~76 ke V) may interfere with quantitative results. Allowance must be made for these effects, or the radiation suppressed; a satisfactory means of absorbing this radiation is covering the exposed lead with cadmium sheet 0.06 to 0.08 inch thick, and then covering the cadmium with copper 0.02 to 0.04 inch thick.

[2] Only those photon emissions having an abundance ≥1% are normally included.

Principal Photon Emissions	Energy (ke V)	Photons per 100 Disintegrations
[3] The K notation refers to X-ray emissions. [4] The weighted mean energies and total intensities are given for groups of photons that would not be resolved by a NaI(Tl) detector. [5] For this photon intensity to be usable, all emitted positrons must be annihilated in the source material. [6] Cascade.		

Calculate the gamma-ray emission rate from the equation:

$$\Gamma = A_s b$$

in which A_s is the activity, in disintegrations per second, of the standard used, and b is the number of gamma rays per disintegration at that energy. Accurately measure quantities of standard solutions of each radionuclide into identical containers, and determine the fractional photopeak area (F) for each of the standards.

Using the equation $\varepsilon_p = F/\Gamma$, calculate the photopeak efficiency, ε_p, and construct a log-log plot of ε_p versus the gamma-ray energy as shown in *Figure 4*.

The mixed image cannot be displayed. The file may have been moved, renamed, or deleted. Verify that the link points to the correct file and location.

~~DETERMINATION OF SPECIMEN ACTIVITY—In the same manner as in the preparation of the calibration curve, determine the fractional area (F) of the principal photopeak of the specimen under assay or an accurately measured aliquot adjusted to the same volume in an identical container as used for the standards. From the calibration curve, find the value of ε_p for this radionuclide. Using the equation $\Gamma = F/\varepsilon_p$, calculate the gamma-ray emission rate (Γ). Calculate the activity (A), in disintegrations per second, of the specimen using the equation $A = (\Gamma/b)(D)$, in which b is the number of gamma rays per disintegration and D is the dilution factor. To obtain the activity, in μCi or mCi, divide A by 3.7×10^4 or 3.7×10^7, respectively. The above relationship is equally valid for obtaining the activity of an undiluted specimen or capsule; in this case, the dilution factor, D, is unity.~~

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; and a glossary.

2. PERSONNEL TRAINING AND DOCUMENTATION

Qualification of instruments and personnel training should be completed in accordance with written policies and/or procedures. Documentation of the qualification of instruments and 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

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 repair. 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. 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 min.

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 should be recorded at least once on each day of use, or more frequently if necessary, using the most common radionuclide setting. The background radiation level should be determined and recorded at initial installation, and periodically verified. 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 due to 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 for multiple radionuclides, two or three different radioactive calibration sources should be included to cover the 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 position 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	NA
System electronics	Yes	NA
Clock accuracy	Yes	NA
High voltage	Yes	NA
Zero adjust	Yes	NA
Background response/contamination check	Yes	NA
Radioactive calibration source (constancy and relative response)	Yes	NA
Accuracy	See footnote [b]	Yes
Reproducibility (precision)	See	Yes

Parameter	Daily[a]	Annually (at a minimum)
	footnote [b]	
System linearity	See footnote [b]	Yes
Supplier equivalence	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 since 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 since their emitted energy (511 keV) is the same for each radionuclide. 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.

7. 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 essentially ^{4}He 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 essentially electrons.

Beyond-use date: Date (and time, if appropriate) that establishes a limit for the use of a compounded preparation. The acceptable use period (i.e., the period of time between the date and time of compounding and the beyond-use date and time) is based on a knowledge of the radioactive properties of the preparation, the results of stability studies on the preparation, and, as appropriate, the assurance of sterility of the compounded sterile preparation.

Bremsstrahlung: Electromagnetic radiation produced by the deceleration of a charged particle through interaction with another charged particle, typically an electron and an atomic nucleus, respectively. The moving particle (e.g., beta particle) loses kinetic energy, which is converted into photons (X-rays). This electromagnetic radiation exhibits a continuous spectrum, with peak intensity a function of the energy of the incident particle.

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.

Carrier-free: A preparation free from stable isotopes of the same element as the radionuclide.

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).

Expiration date: Date (and time, if appropriate) that establishes a limit for the use of the manufactured product, which is based on the knowledge of the radioactive properties of the product and the results of stability studies on the finished dosage form.

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 min (cpm) or milliroentgen per h (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: 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.

No-carrier-added: A preparation where no stable isotopes of the same element as the radionuclide being tested are intentionally added in the stated chemical form or at the position of the radionuclide in the molecule being tested.

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 by radioactive decay. 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 (US 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.

Specific activity: The radioactivity of a radionuclide per unit mass of the element or compound. The unit of specific activity is radioactivity per mass expressed on a gram or mole basis [e.g., mCi/µg (MBq/µg), Ci/mmol (GBq/mmol)]).

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.

8. REFERENCES

American Society for Testing and Materials (ASTM) D3648. Standard practices for the measurement of radioactivity. West Conshohocken, PA: ASTM International; 2011.

American Association of Physicists in Medicine (AAPM). The selection, use, calibration, and quality assurance of radionuclide calibrators used in nuclear medicine. AAPM, College Park, MD; June 2012. Report No.: 181.

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SWS WORKFLOW VALIDATION

XML Attribute	XML Value	SWS Attribute	SWS Value	Notes
No validation errors found				

* ~~These certified reference standards are obtainable from the National Institute of Standards and Technology, Washington, DC 20234.~~