3 Non-imaging and Radiopharmacy Instrumentation in Nuclear Medicine

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3.1 Introduction

Non-imaging radiation detection and measurement instruments are of massive importance in nuclear medicine practice. This section illustrates a review on basic principle, performance, application, and the recent quality control recommendations for those of particular usage and daily applications. Three major categories are covered including non-imaging equipment, radioactive reference sources, and radiopharmacy equipment and tools. Non-imaging equipment category includes dose calibrator, well counter, thyroid uptake probe, intraoperative probes, survey meters, area monitors, and CT dosimetry toolkits. The second category of tools used in nuclear medicine is an array of radioactive reference sources that are commonly used in calibration and daily quality control and assurance. The last category covered radiopharmacy laboratory equipment including laminar flow safety cabinet, high-performance liquid chromatography (HPLC), thin layer chromatography scanner, gas chromatography, gamma spectrometers, pH meter, and specialized tools for the determination of bacterial endotoxins. More details of these equipment could be found in other specialized references and textbooks.

3.2 Non-imaging Equipments

3.2.1 Dose Calibrator

In nuclear medicine departments, usage of a dose calibrator is a must. Prior to each radiopharmaceutical injection or administration, the radioactivity

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of such a prescribed radiopharmaceutical has to be well assayed and measured using the dose calibrator. It is a calibrated re-entrant ionization chamber filled with argon gas under pressure (typically 1–2 MPa or 10–20 atm), coupled to a high-voltage power supply and an electronic circuit that converts and displays chamber response.

The chamber is a well type (close to 4π geometry), and the wall of the chamber is a thin aluminum. It contains two electrodes having an electric potential between them. When a beam of ionizing radiation passes through the chamber, it produces electrical charges that are collected by positive (anode) and negative (cathode) electrodes forming total amount of current (time-averaged ionization current). Ionization current is measured using sensitive current-measuring devices called electrometers with a fixed time constant and converted to a voltage signal, which is amplified, processed, and displayed in digital form in units of radioactivity.

The dose calibrator chamber is usually provided with at least 6 mm lead to eliminate the background radiation that may be present in the working environment. This shielding also provides protection to the operator by minimizing the exposure rate resulting from the radioactivity being used and also prevents efficiency changes caused by scattering material in the vicinity. It is important to note that the shielding setup upon installation should remain the same after the calibration is carried out and any changes to that setup affect the calibration results.

A sample holder of low z material is provided into which a vial or syringe can be placed to ensure that it is positioned optimally within the chamber and to ensure reproducibility and consistency of the measurements if the same or different sample is inserted. The dose calibrator may include a printer to document the activity measurements or an RS-232 serial communications port or Universal Serial Bus (USB) port to interface the calibrator to radiopharmacy computerized management systems.

The dose calibrator can be calibrated by the manufacturer for the commonly used radionuclides in medical facility. The calibration is being done through comparison with an appropriate standard activity that is directly traceable to a national primary standard. Using the primary or traceable standard sources, a calibration factor for the ionization chamber can be determined for each specific radionuclide. These calibration settings are then saved within the system for each specific radionuclide.

The use of dose calibrator in a medical facility should serve to provide reliable measurements of the radioactivity being assayed. However, some uncertainty within these measurements can be detected ($<0.0 \pm 5\%$) and dosage limit to the prescribed dose is ($<\pm 10\%$). For such a reason, the dose calibrator has to be under quality system to ensure the reliability of the readings (see Table 3.1). Sources of such uncertainty can be caused by the fact that the calibration settings are made upon certain source geometry, volume, material type and thickness, and position in the chamber. The calibration factor can also be affected if a different container type (e.g., syringe) is used which affects the readings.

Also, the type of material of the container can contribute to uncertainty of the reading due to self-absorption that could occur on the surface of the container. This is significant in beta emitter radionuclide, and since the energy starts from 0 till the maximum transition, the sensitivity of the dose calibrator to beta emitter radionuclide is low. Further common sources of uncertainty are high activity and the increase of probability of ion pair recombination, chamber shielding, possible errors in calibration, and the differences between the standard calibration containers and other types [2, 3].

It is crucial for the operator to understand the importance of the correct choice of the radionuclide before measurement as the dose calibrator itself would not be able to recognize the type of the radionuclide within the container. However, the reading will be done automatically in units of activity (Becquerel or curies). Table 3.2 compares between two different commercially available dose calibrators.

Table 3.1 Routine quality control tests for a dose calibrator

Routine test	Purpose	Acceptance	Daily	Monthly	Annually
Physical inspection	Check whole system including source holders, cables, and other accessories for damage	✓	✓	✓	✓
High voltage	Check system constancy and correct operating voltage	✓	✓	✓	✓
Clock accuracy	Check that the calibrator clock is the same as the time of day	✓	✓		
Zero adjustment	Check that the display is at zero when no radioactivity is present	✓	✓	✓	✓
Background counts	Check background response under operational conditions appropriate for a particular radionuclide; to detect contamination	✓	✓	✓	✓
Constancy (relative response)	Check the stability and reproducibility of the ionization chamber, electrometer, and calibrator nuclide settings Using long lived source (e.g. Cs-137) absence of any radioactive impurities. Relative chamber response has to be monitored for any drift	✓	✓		
Stability	Check the short-term counting precision	✓			✓
Accuracy	Check the accuracy of the activity reading	✓			✓
Linearity	Confirm that the calibration setting for a particular radionuclide indicates the correct activity over the entire range of use	✓			✓
Subsidiary calibrations	For containers and volumes with no calibration factor provided by the manufacturer	✓			✓

Data are adapted from [1] with permission from Springer Publishing

3.2.2 Well Counter

Well counter is routinely used in nuclear medicine laboratories including research, clinical applications, as well as for radiation protection purposes. It is one of the most sensitive detectors for gamma rays. It consists of a single solid cylindrical crystal of thallium-doped sodium iodide-NaI (Tl) (at least 2 × 2 in., with a 3/4-in. diameter well about 1–1/4 in. deep) detector with a hole in the center for a sample to be placed. The crystal is surrounded by thick lead shielding around 5 cm or greater to minimize the background due to ambient radiation [6]. The sample can be collected for certain volume or shape in a tube, other kinds of sample could be blood, urine samples, or wipes from surveys of removable contamination.

The well counter consists of the cylindrical scintillation crystal (well type) coupled to photomultiplier tube (PMT) in connection with other electronics such as preamplifier, amplifier, pulse-height analyzer (PHA), and scalar timer. A well counter is an extremely sensitive detector. The counting results can be expressed on activity in the range of micro curies (~100 kBq). At higher activities, serious dead time problems do emerge, leading to count rate underestimation.

3.2.3 Thyroid Gamma Probe

Thyroid gamma probe is categorized under the well-known radiation measurements and counting detectors known as thyroid uptake probe. The thyroid uptake is measuring the fraction of an administered amount of radioactivity that accumulates in the thyroid at selected times following oral administration of ^{131}I-iodide,

Table 3.2 Specifications of two widely used dose calibrators[a]

Specifications	Capintec CRC	Atomlab 500
Ionization chamber dimensions	26 cm deep × 6 cm diameter	15.24 × 39.37 cm diameter
Measurement range	Auto-ranging from 0.001 MBq to 250 GBq	Auto-ranging from 0.0004 MBq to 3700 GBq
Nuclide selection	8 pre-set, 5 user-defined (80 radionuclide calibrations in memory)	12 pre-set, user-defined (98 radionuclide calibrations in manual)
Display units	Bq or Ci	Bq or Ci
Electrometer accuracy[b]	<±2%	±1% or 0.2 μCi, whichever is greater.
Response time[c]	Within 2 s	1–2 s for doses greater than 200 μCi; 3 s for doses greater than 20 μCi
Repeatability[d]	±1%	±0.3% above 1 mCi short term (24 h)

[a]Source: [4, 6]
[b]Electrometer accuracy: electrometer's measurement of current is traceable to primary standards
[c]Response time: time to convert and display the ionization current into an indication of the activity (MBq)
[d]Repeatability: the precision with which a single measurement is made

^{123}I-iodide, or ^{99m}Tc-pertechnetate. Commercially available thyroid uptake probes are generally supplied as integrated, computerized systems with automated data acquisition and processing, capabilities, yielding results directly in terms of percent uptake (see Fig. 3.1). The thyroid probe shown typically consists of a wide aperture, diverging collimator, a 5-cm thick × 5-cm diameter sodium iodine NaI(Tl) crystal with an open cylindrically shaped, PMT, preamplifier, amplifier, an energy window, and a stand gantry. Figure 3.2 demonstrates the probe collimator and other connected components.

Determination of thyroid uptake includes measurement of counts collected for 1 min over the thyroid gland. Another measurement is then taken over the patient's mid-thigh for 1 min and at the same distance (e.g., 20–30 cm), taking care to exclude the urinary bladder from the detector field. A source of the same radionuclide of identical activity to that given to the patient is placed in a standardized neck phantom, shown in Fig. 3.3, and again counted for 1 min using the same geometry. The room background is also counted for 1 min with the neck phantom with no radioactive material inside the room or the phantom. This approach is known as the two-capsule method, since one ^{131}I capsule is administered to the patient while a second, identical capsule serves as the standard and is counted with each uptake measurement [5, 7].

Alternatively, the radioiodine capsule can be counted in the neck phantom before oral administration, and the counts obtained can be corrected for decay at each patient counting session. This later approach is named one-capsule method [6]. The radioiodine uptake (RAIU) is then calculated using the following relationship:

$$\text{RAIU} = \frac{\text{Neck counts} - \text{Thigh counts}}{\text{Phantom counts} - \text{Background counts}} \times 100\%$$

The time of measurement is approximately 24 h after the radiopharmaceutical administration. An additional uptake measurement may also be performed at 4–6 h, particularly in cases of suspected rapid iodine turnover.

The routine quality tests that can be performed to implement quality assurance of thyroid uptake probe are many and can be summarized as follow. The operator must check all physical parts, collimator checks, probe mounting, and cable connections for any possible defect before using the equipment. Background count rate needs also to be checked. It is helpful to identify the count rate level in the absence of the sample and to detect any possible contamination in the area.

Operating voltage constancy and accuracy must also be performed before using the probe. Sensitivity and energy spectrum have to be inspected, and the energy window must be centered on the photopeak. System stability looks at short-term counting precision of the equipment and can be performed every 6 months [1]. The use of gamma camera method in measuring thy-

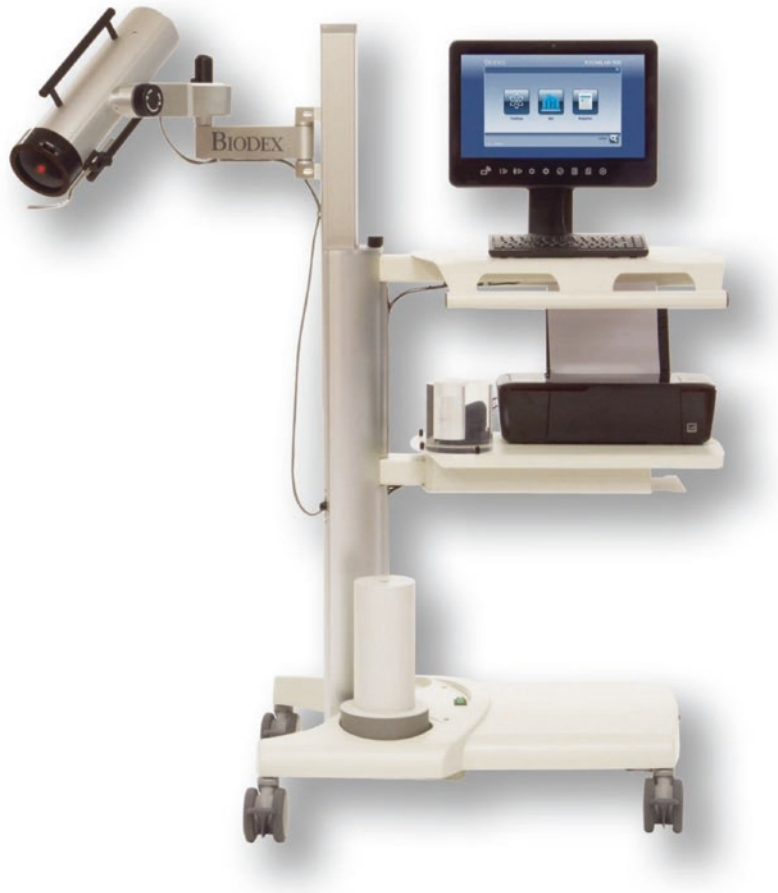


Fig. 3.1 A photograph of Atomlab™ Thyroid Uptake System, showing one example of thyroid uptake probe interfaced to computer system (PC) and printing facility. (Reproduced with permission)

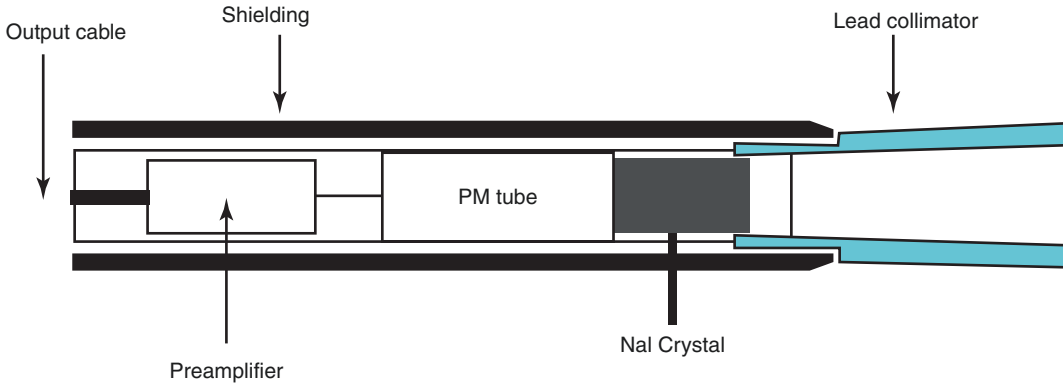


Fig. 3.2 Components of thyroid uptake probe

roid uptake using iodine-131 capsules has been proposed as an alternative providing measurements as accurate as the thyroid uptake probe [8]. However, gamma camera method requires validation versus known standards.

3.2.4 Intraoperative Probes

In early days of nuclear medicine practice, the intraoperative probe was a Geiger–Müller (GM) counter detecting phosphorus-32. In 1956, Harris

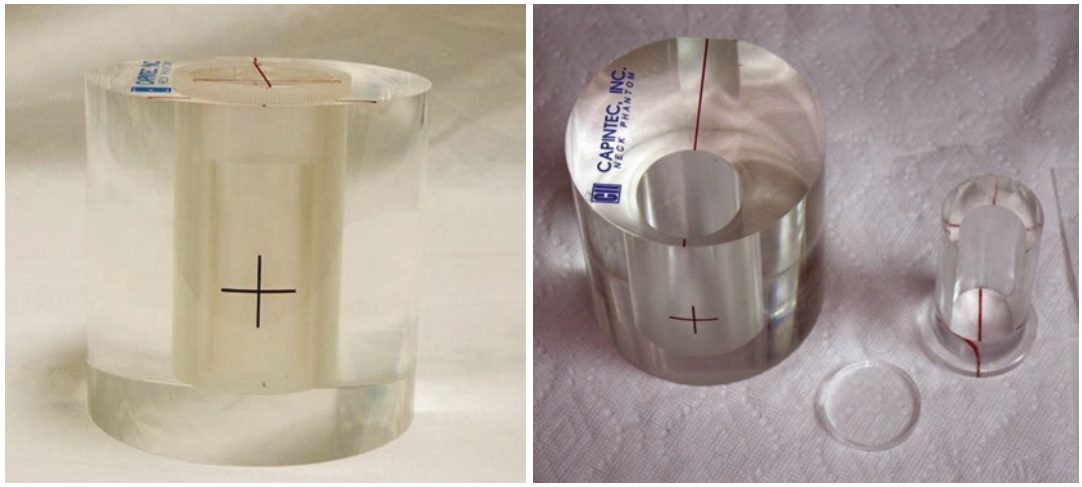


Fig. 3.3 The CAPTUS neck phantom is made of clear Lucite designed to represent a patient's neck (Mirion Technologies, Capintec, Inc., with permission). It has a two-part insert that allows counting from a bottle, vial, or capsule. A capsule holder is supplied to enable the user to count capsules directly, without having to dissolve them

et al., at the Oak Ridge Institute of Nuclear Studies Medical Hospital, reported the first radioguided surgery involving gamma detection probe systems [9]. They used a handheld scintillation detector device to detect gamma rays from ^{131}I that had been administered to a patient with differentiated thyroid cancer. Nowadays, intraoperative probes are widely used in the management of cancer and within the practice of surgery.

The intraoperative probe is a small handheld counting device for tumor localizations and removal in surgery. After the administration of a radiopharmaceutical that accumulates in the tumor of a patient, the surgeon detects the tumor with the intraoperative probe detection sensitivity (i.e., the probe provides the surgeon with an acoustic guide to locate the tumor over the large surgical field) and resects it during the surgery. However, it can be used either as radioguided sentinel lymph node biopsy (SLNB) or radioguided surgical resection of tumors [10].

Intraoperative detectors are categorized into two types: gamma probes that detect photons and beta probes for positron and beta-minus emitters. These detectors can be available as either scintillation detectors (both crystal and plastic types) or semiconductor detectors. A typical schematic diagram for intraoperative probes either scintillator or semiconductor is illustrated in Fig. 3.4. The crystals used in scintillator detector probes can be NaI(Tl), CsI(Tl), cerium-activated LSO, BGO, and cerium-doped GSO. Radionuclides that are of common use are ^{99m}Tc colloid for radioguided SLNB and the positron emitting radionuclide, e.g., (^{18}F) for resection of tumors. The choice of the appropriate detector depends on the surgeon needs and the surgery type. Table 3.3 compares between scintillation crystal and semiconductor-based intraoperative probes.

Recent developments of handheld self-contained gamma detection probes introduced the integrated Bluetooth wireless technology to eliminate the need for cables connecting the probe to the control unit, and to guarantee the comforts of the surgeon. Figure 3.5 shows a schematic drawing of the system.

Various quality control tests for intraoperative gamma probes (in accordance with Standard NEMA NU 3-2004) can be performed to ensure the high performance of this device; these tests include sensitivity test which can be done using pulse rate/activity (cps/MBq) carried out on different distances with selected nuclides and energy window. Measurements are to be carried out in air, in a scatter medium, and through side shielding in air. Also, short-term sensitivity stability can be done for a certain nuclide performing 20

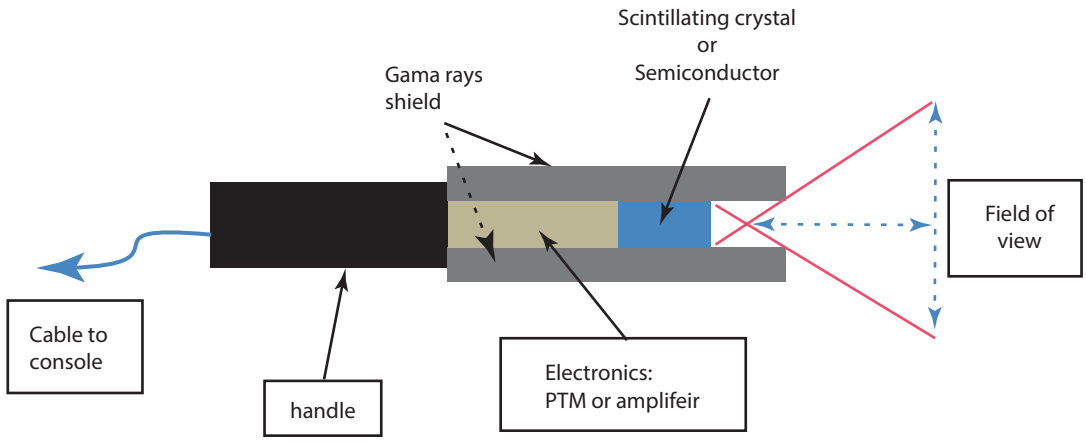


Fig. 3.4 A diagram for a typical design of intraoperative radiation detector

Table 3.3 Comparison between the advantages and disadvantages of scintillation and semiconductor detectors

Scintillator detector	Semiconductor detector
Higher sensitivity	Higher energy resolution
Scatter is relatively significant	Scatter rejection capability
Heavy	Has a very thin entrance window that enables counting of low energy β and γ rays
Poorer energy resolution and scatter rejection	Direct detectors with improved energy resolution
Much bulkier	Can be manufactured in very small sizes and it is expensive

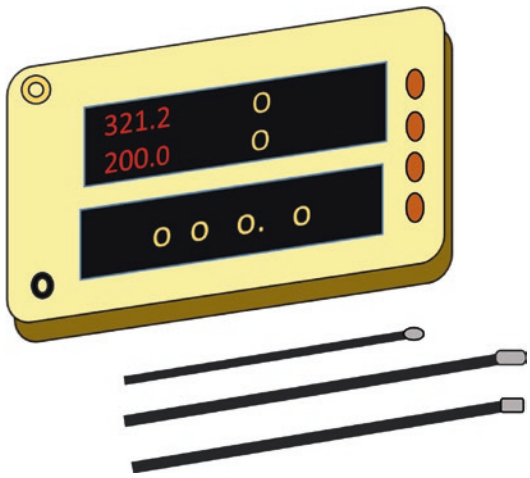


Fig. 3.5 Schematic diagram of intraoperative gamma probe with different probe shapes and geometries

sequential measurements (pulses/selected time), observed, and expected standard deviance and chi-square value to be recorded. Spatial resolution test is carried out to determine the FWHM and FWTM at 30 mm source-detector-distance in water. Count rate capability in a scatter medium is tested by calculating the decay corrected count per time (cps) and comparing it to a reference count value to achieve a control reading within the acceptable range (less than 2 standard deviations from the reference value). Angular resolution in a scatter medium measures the FWHM and FWTM in degrees with 30 mm source–detector distance in water using a selected nuclide and an energy window. Both absolute and relative energy resolution can be performed. Side and back shielding efficiency are also to be tested.

3.2.5 Survey Meters and Area Monitors

In radiation safety practices, there are instruments routinely used to monitor and evaluate the radiation level (exposure rate or counts rate, e.g., contamination). Survey meter is a battery-operated, portable, handheld detector that can be either a gas-filled detector or solid-state detector (scintillator or semiconductor detectors).

Gas-filled detectors generally include ionization chamber, Geiger–Müller (GM) counter and

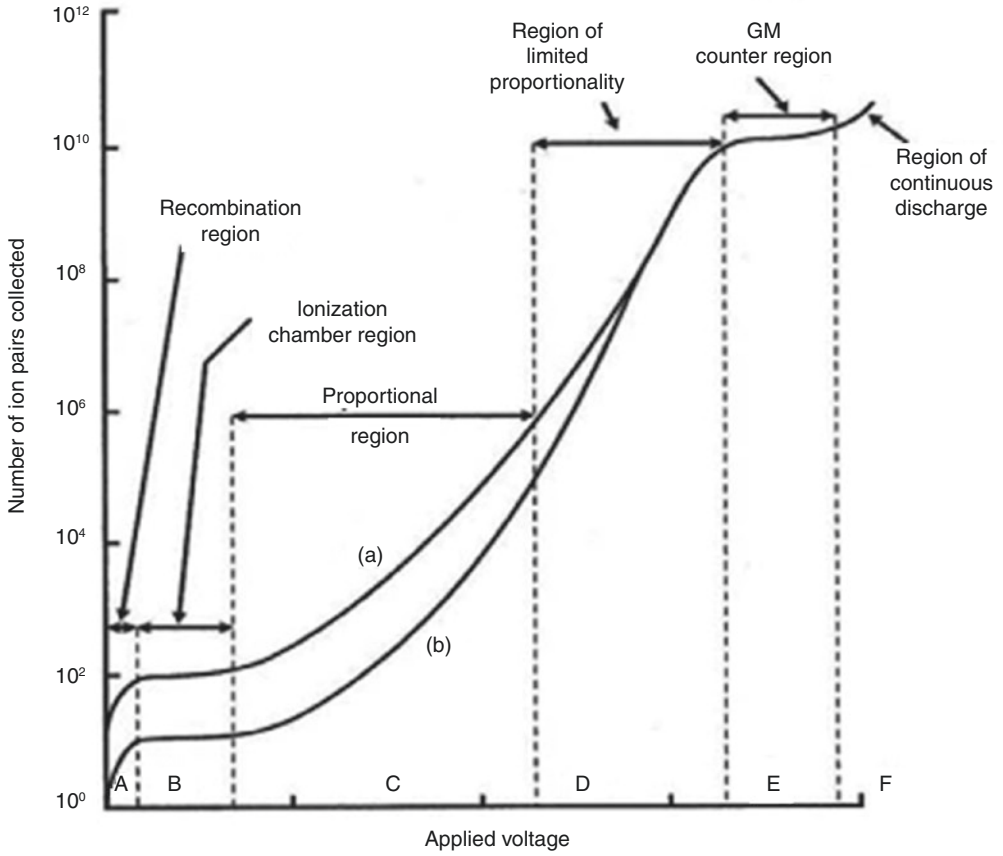


Fig. 3.6 Characteristic regions of gas-filled detectors

proportional counters. Nobel gases are generally used in these detectors. All respond to radiation by means of ionization-induced electrical currents generated in the ionization chamber, but depending on the different design and the voltage applied between the two electrodes, the detector operates in certain region specifying its own type (ionization region B, proportional region C, or Geiger–Müller (GM) region E), shown in Fig. 3.6.

Ionization current is being displayed on a monitor (digital type) or on a front-panel meter. The survey meter can be calibrated to illustrate the units of radiation level as exposure rate (e.g., sievert per hour) or air kerma (gray per hour). The survey meters may cover a range of radiation level measurement from nSv/h to Sv/h, but the typical range in use is μSv/h to mSv/h. Depending upon the electronics used, detectors can operate in a "pulse" mode or in the "mean level" or current mode. Proportional and GM counters are normally operated in the pulse mode. Since ionization detector operates in the current mode, it is suitable for high-dose rate measurement, due to its relatively flat energy response and air kerma rate independence [11].

Geiger–Müller (GM) operates on pulse mode (which means that the signal pulses have the same amplitude regardless of the energy of the incoming radiation) and under high potential difference providing a high electron amplification factor, and thus, GM has a high sensitivity. Therefore, GM can be well suited for low-level surveys, for example, monitoring for radioactive contamination. Further, uncompensated GM detector can be used for evaluating the barrier thickness of a monoenergetic source. For energy discrimination, end window GM counters have a

removable buildup cap to discriminate β from γ rays. For β measurements the end cap must be removed to allow β particles to enter the sensitive volume.

Solid state scintillator detector (composed of organic and non-organic solid crystals, e.g., NaI(Tl)) converts the energy of the incoming gamma rays into light, these detectors use non-air-equivalent crystal as the detection medium, thus suitable for gamma rays (measure only the count rates). However, it is able to capture specific spectroscopic profiles and identify the measured radioactive materials. On the other hand, solid state semiconductor detectors can be intrinsic (very pure material) and extrinsic or doped. The most common semiconductor detector made of silicon (Si) or germanium (Ge) crystal suitable for both the gamma ray and the X-ray detections (operates similar to ion chamber, create electron-hole pairs instead) and convert the incoming energy into electrical pulses; their sensitivity is about 10^4 times higher than that of gas filled detectors [12].

The most common neutron survey meter gas-filled detector type are proportional counters, ionization chambers, and fission chambers. The detection of neutrons in theses detectors can be thermal through nuclear reaction, fast neutron via recoil interaction, and/or detection of neutrons that induce fissions in fissionable material (e.g., uranium) coated inside the inner wall of the chamber. Detectors filled with BF_3 and ^{3}He gases are thermal neutron detector type, which operate in the proportional mode, and have sufficiently large cross sections and high Q-values to convert slow neutrons with high probability into charged particles with enough kinetic energy to exceed detection thresholds. In case of ^{4}He- and CH_4-filled detector which called the fast neutrons detectors, neutrons produce light recoil nuclei (hydrogen) to ionize the gas in the tube. Moreover, detector lined with a boron (^{10}B) compound plated on the inside of the wall is considered as proportional counter where neutrons detection rely on boron coating compound causing an $(n, \propto)$ reaction, and the $\propto$ particles can easily then be counted or detected by their ionizing interactions current [13, 14]. All survey meters should be calibrated using a reference instrument that is traceable to a national standard laboratory.

Area monitors are importable instruments being fixed individually in a selected location for monitoring the radiation level within that specified area or facility. This instrument provides an audible and visible alarm types to warn the personnel within the area of the high radiation level if detected. The data of such monitors can be displayed on the monitor itself, and the data is integrated to master computer station, which is continuously monitoring the different areas through a special graphical/digital user interface that report the rooms reading in the selected unit (e.g., μSv/h). These devices may be known as gamma probes, ion chamber detector, or compensated GM counter detector type (see Fig. 3.7).

3.2.6 CT Dosimetry

The advent of X-ray computed tomography (CT) in hybrid nuclear imaging devices have received particular interest in the last two decades. CT scanner design with new features and capabilities have significantly been improved over the years, thanks to the amazing rapid developments in CT technology. This in turn contributes to the implementation of many new clinical applications based on CT which continues to grow, often by 10–15% per year [15]. However, the CT dose becomes a demanding concern in radiation protection and dose optimization to control radiation exposure within the CT applications.

The use of CT dose index (refereed as CTDI) is a useful tool for CT dose measurement and optimization protocols. By using CT pencil ionization chamber of sufficient length (100 mm is most commonly used) to cover the CT dose profile, one can estimate the delivered CT dose to phantoms of standard dimensions at several locations.

Phantoms adopted by the US Food and Drug Administration (FDA) were a 32-cm-diameter cylindrical acrylic phantom to represent an adult abdomen and a 16-cm-diameter version to represent an adult head or small pediatric bodies. Both of the phantoms are 15-cm thick (in the z-axis

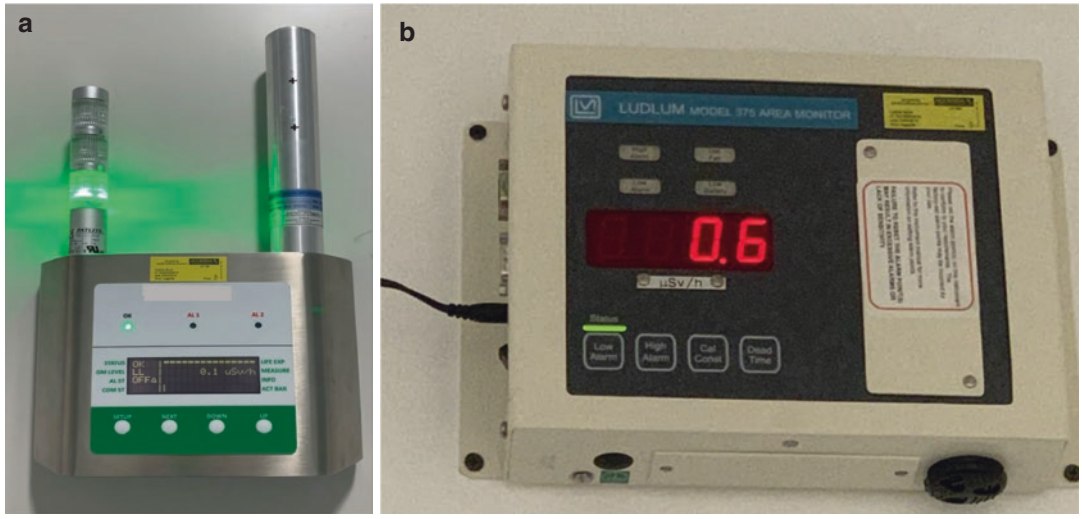


Fig. 3.7 Digital area monitor from different manufacturers. (**a**) Gas-filled detector type 2 energy compensated Geiger–Müller tubes for low and high dose rate measurements manufactured by a previous vendor named MecMurphil, Italy. (**b**) LUDLUM area monitors that incorporate an internally energy compensated GM. (LUDLUM measurements, Inc., with permission)

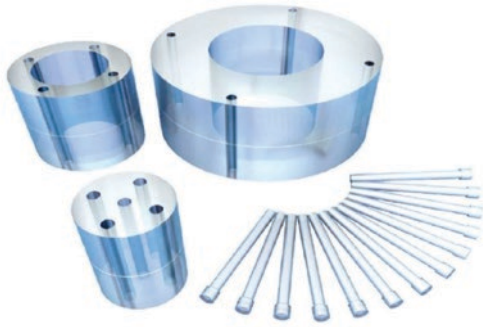


Fig. 3.8 CT scan test phantom/head/whole body/pediatric. RaySafe, CT Fluke Biomedical. (Image credit of RaySafe, Sweden, with permission)

direction) and contain several 1-cm-diameter holes for the insertion of the ionization chamber. The holes are at the center of the phantom and at a 1-cm depth at the 3-, 6-, 9-, and 12-o'clock positions (referred to as the peripheral sites). Figure 3.8 shows one commercial set used in CT dosimetry calibration.

CTDI can be defined as the z average dose (to the phantom location at which it is measured) from a complete series of slices (either axial or helical scan). The CTDI can be measured using calibrated electrometer and pencil ionization chamber of 100 mm length known as $CTDI_{100}$. The dose measurements differ from the center to the peripheral locations within the body phantom because of the scattering dose getting increased toward the center, further, the ionization chamber includes the tails of dose profile and therefore both the primary and the scatter radiation are being included. $CTDI_w$ quantity is that combines both the values measured at the center and the periphery locations within the standard phantom. The dose quantity $CTDI_{vol}$ takes into account the helical pitch or axial scan spacing and can be displayed by the CT system console in front of the operator. Table 3.4 displays important quantities and definitions used in CT dosimetry.

When irradiating patients during several examinations, the dose delivered is a major concern. Dose length product (DLP) is a term used to represent the amount of radiation delivered to the patient

Table 3.4 Terminology used in X-ray computed tomography (CT)

Quantity	The International Electro Technical Commission (IEC)
Measured free-in-air	
CT air kerma index	$\mathrm{CTDI}_{\mathrm{air}} = \frac{1}{NT}\int_{-\infty}^{\infty} K_{\mathrm{a}}(z)\,\mathrm{d}z$
Measured in standard phantom	
Weighted CT air kerma index	$\mathrm{CTDI}_{\mathrm{w}} = \frac{1}{3}\mathrm{CTDI}_{100,c} + \frac{2}{3}\mathrm{CTDI}_{100,p}$
Normalized weighted CT air kerma index	$n\mathrm{CTDI}_{\mathrm{w}}$
Volume CT air kerma index	$\mathrm{CTDI}_{\mathrm{vol}} = \mathrm{CTDI}_{\mathrm{w}} / \mathrm{pitch} \quad \mathrm{pitch} = \frac{1}{NT}$
CT air kerma—Length product	$\mathrm{DLP} = \mathrm{CTDI}_{\mathrm{vol}} \times L$

N = actual number of data channels used during one axial acquisition, T = width of each channel ($N \times T$ = nominal radiation beam width), L = is the total z-direction length of the examination

by calculating the $\mathrm{CTDI}_{\mathrm{vol}}$ multiplied by the whole examination length. However, the probable risk to the patient cannot be determined unless a radiosensitivity factors of the irradiated tissues/organs are taken into account to derive what is called effective dose, E [16] (see Chap. 9 for further details).

3.3 Standard Sources

To ensure a high level of performance of nuclear medicine instrumentations, reliability and accuracy of measurements need to be continuously verified and checked. Therefore, there are long-lived reference sources that are needed to support many periodical quality assurance procedures. Reference sources are often sealed, long-lived radionuclides, and can be ordered with various activities and geometries from commercial vendors. These sources must be traceable to a national standards dosimetry laboratory; traceability helps ensure the accuracy of the calibrated activity. National primary standards are maintained by the relevant National Metrology Institute (NMI), such as the National Physical Laboratory (NPL) in the UK, the National Institute of Standards and Technology in the USA, and the Australian Nuclear Science and Technology Organization (ANSTO) [2]. However, the world measurement standards authority, Bureau International des Poids et Mesures (BIPM), organizes the process of standard comparison between the NMIs to confirm the accuracy of its standards. Another organization helping the cooperation between NMI within the European region is the European Association of National Metrology Institutes (EURAMET), who (beside other activities) also organizes comparative measurements. A number of standard sources that frequently used in quality assurance/quality control of nuclear medicine equipment will be discussed.

3.3.1 Reference Radioactive Sources

The National Institute of Standards and Technology (NIST) is the national metrology institute of the USA which provides physical measurements and standards in a variety of fields and industries with expansion developed to include the medical imaging. Particularly in radiation and radioactivity standards, radioactive standards reference material (SRMs) has been developed and produced and source calibrations are performed to guarantee the traceability for radiopharmaceuticals being used in medical imaging to ensure the accuracy and precision of the quantitative measurement within the medical modalities related to patients. NIST provides a framework for traceability through establishing primary standard, developing secondary standards, and disseminating those standards [17].

3.3.2 Gamma Camera Reference Sources

Standard radioactive sources are important accessories for performing daily quality control tests in nuclear medicine departments. As explained in Chap. 11, gamma camera and SPECT systems need a comprehensive quality assurance program that maintains clinical images of high quality and accurate diagnostic performance. Uniformity test of SPECT system describes the degree of uniformity of count density in the image when the detector is flooded with a spatially uniform flux of incident photons. Uniformity test can be performed using either fillable flood source or ^{57}Co flood sheet source. The flood source is a long-lived radionuclide in the form of an extended sheet of plastic, with photon energy (i.e., 122 keV) similar to the most commonly used in clinical practice, 140 keV.

Fillable flood source is a sheet of Perspex that is filled with water and ^{99m}Tc pertechnetate. The preparation of the phantom is advised to be carried out with radioactive range of 10–15 mCi at time of filling. The use of such source requires a preparation and care during the filling to ensure uniform/homogenous mixing and also to ensure that the phantom is free of air bubbles that may result due to shaking and filling. The solution should be refilled regularly after the phantom, wash with water and diluted sodium hypochlorite in order to avoid growth of algae, which can bind with ^{99m}Tc compounds, causing hot artifacts [18].

Some limitations of the fillable flood source usage are the exposure due to radiation during the preparation as well as the time consumed to make sure of the suitability of the phantom. Phantoms with thick walls and a large volume have shown an increase in counts in the center of the FOV, which is possibly due to scatter and septum penetration (depending on the collimator and radionuclide used).

The ^{57}Co flood source is a sealed sheet that is commercially available and comes at desired activity up to 15 mCi. It is very convenient for daily quality control tests due to handling simplicity and relatively long half-life (270 days). However, a caution needs to be taken while handing the source, especially newly purchased, due to contamination of other isotopes including ^{56}Co, ^{58}Co, and ^{60}Co impurities. An operator may therefore experience some artifacts or failure of the routine daily uniformity test whenever a new ^{57}Co flood sheet source is used, that could disappear as time passes due to radioactive decay. Also, high count rates and pile-up effects from the scatter and septum penetration of the high energy photons may contribute to alternation of the test results. These problems can be avoided by using less count rate sources and maintain a distance between the source and the detectors at least 15 cm.

3.3.3 PET Scanners

In PET, primary sources and calibrated phantoms and methods have been introduced for improving image consistency and quantification accuracy. ^{18}F and ^{68}Ge are common radionuclides used in calibration of PET instrumentation. NIST developed primary activity standards for positron emitter radionuclides such as ^{18}F through various methods, but due to the short half-life of ^{18}F (109.8 min), it was not possible to be prepared for distribution [19]. As a result, ^{68}Ge/^{68}Ga source (half-life 270.9 days) was introduced as a reasonable surrogate of ^{18}F to be used for calibration by applying appropriate correction factors. Such correction factors would strongly depend on the instrument and the geometry in which the source is measured. Dose calibrator calibration methodology has been established using the ^{68}Ge-based calibration sources (syringe) for the calibration of dose calibrators for the measurement of ^{18}F [17].

Calibration methodology is developed for large ^{68}Ge solid PET phantoms, making traceable phantoms commercially available. NIST established a prototype of large volume (30 cm length × 20 cm diameter, approximately 9 L) of solid ^{68}Ge cylindrical phantom in epoxy as a surrogate for ^{18}F. This phantom has a calibrated value for the amount of ^{68}Ge that is directly traceable to a national standard. Similarly, NIST provides calibration of other epoxy ^{68}Ge phantoms of other manufacturers. These phantoms can be used for calibration and monitoring performance

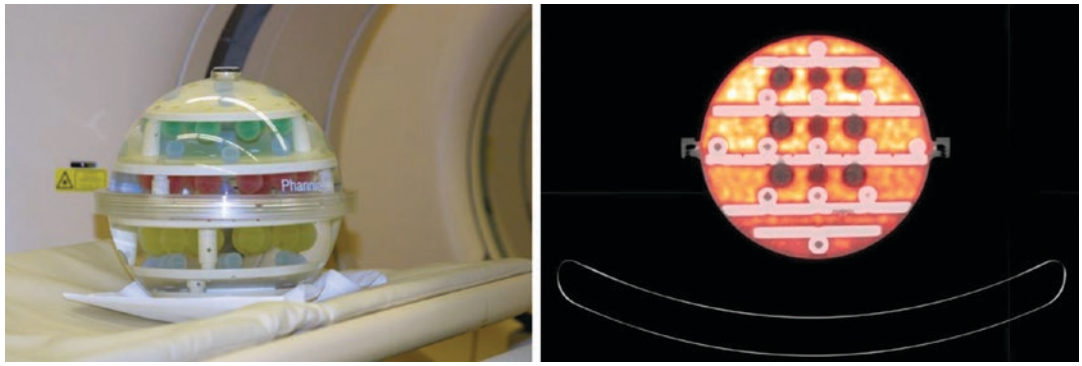


Fig. 3.9 NIST's first standard phantom for calibrating the PET-MR machines. This phantom consists of a plastic sphere about the size of a person's head filled with grids of smaller plastic spheres containing salt solutions that become magnetized in a magnetic field. Also includes a small, calibrated amount of fluorine-18 (^{18}F); a PET image shows the glowing of ^{18}F inside the phantom [20]

of the scanners during clinical trials in a way that is traceable to national standards.

Other efforts are still going on for PET/MR phantom design and calibration which includes future inserts of calibrated samples of solid, longer-lived radioactive sources such as solid ^{68}Ge hemispheres or discs, and an improved filling system that will make it easier and faster to introduce radioactive background solutions. Figure 3.9 shows NIST approach to tackle this issue.

3.4 Radiopharmacy Equipments

Radiopharmaceuticals require a well-designed quality program during production and preparation steps to assure the high quality of the final product. The quality program should specify and meet the acceptance limit set forth by national and/or international guidelines. The preparation procedures should be performed under certain conditions of microbial and particle contamination. Laminar flow and safety cabinet can verify these conditions of sterility for certain types of radiopharmaceuticals preparation. Further, quality control procedures are required to ensure that the final product is complying with standard specifications of this specific radiopharmaceutical. High-performance liquid chromatography (HPLC), thin layer chromatography (TLC), gas chromatography (GC), and gamma spectrometer are among the most important tools mainly required for radiopharmaceutical quality assurance purposes.

3.4.1 Laminar Flow Safety Cabinet

Most radiopharmaceutical administrations are injected through intravenous injection. To avoid microbiological contamination, particulate or pyrogens insertion into finished product, and to ensure radiation protection principles, radiopharmaceutical preparation should be carried out in a designated shielded area under aseptic condition or laminar flow cabinet (LAFC) [21, 22]. Laminar flow is defined as airflow in which the entire body of air within a confined area moves with uniform velocity along parallel lines with a minimum of eddies [21]. By design, laminar flow aims to maintain uniform velocity and direction of air flow at any cross section. Further, all air entering the system must be filtered by means of high-efficiency particulate air (HEPA) filter. Laminar flow safety cabinet provides three types of protection, namely personnel, environment, and product from airborne contamination or particles. Laminar flow safety cabinet should meet the classification criteria based on construction, airflow velocity, and pattern and exhaust system [23]. There are several international standards for bio-

logical safety cabinets, among these are the following major international standards [23].

1. American Standard (National Sanitation Foundation) NSF 49
2. European Standard EN 12469
3. Australian Standard AS 2252
4. Japanese Standard JIS K 3800

The main role of laminar flow is to protect personnel, product, and environment. Hence, air filtration and air flow patterns should be considered by design to avoid cross contamination. Therefore, safety cabinet provides a clean air into working area and prevents airborne particles from entering the semi-enclosed work space, i.e., the clean air chamber. The clean air environment is based on high-efficiency particulate air filtration and uniform parallel air flow. The HEPA filter consists of a boron silicate or fiberglass microfiber membranous filter that is folded back and forth across corrugated aluminum separators. The separators on both sides of the filter act as baffles to direct the air in a laminar air flow (i.e., a uniform parallel flow without turbulence) [24]. The filter efficiency is at least 99.97% for particles size 0.3 μm or larger. The efficiency should be 99.997% for strict sterile conditions. However, gases and vapors are not trapped, but particles and liquid droplets are removed. The HEPA filter cannot be cleaned and must be replaced once it is loaded to its capacity as indicated by filter testing [24].

There are three major types of laminar flow: safety cabinets I, II, and III.

Class I safety cabinet is the basic design of safety cabinet, provides personnel and environment protection. The air filtration system consisting of per-filter and a HEPA filter. Class I safety cabinet is the most proper for biosafety levels 1, 2, and 3. As there is no product protection, it has limited applications.

Class II safety cabinet is a vertical laminar, providing descending downward unidirectional HEPA filtered air with continuous supply into the cabinet. Hence, it protects the product or sample from contamination. Class II safety cabinet is divided into two types: class II type A and type B.

The main difference among class II subcategories is the percentage of the extracted to circulating air (Fig. 3.10). Type A is recirculating air with a minimum exhaust 30% of HEPA filtered air into the laboratory. However, in type B, the percentage of recirculating air is reduced to 30% (Type B1) or totally removed (Type B2). Further, the route of discharge or exhaust; some cabinets may exhaust into the laboratory through HEPA filter, others (class II type B2) require designated duct to be connected to outside the building. The latter type is considered as a total exhaust system and does not recirculate air to the laboratory, which is more

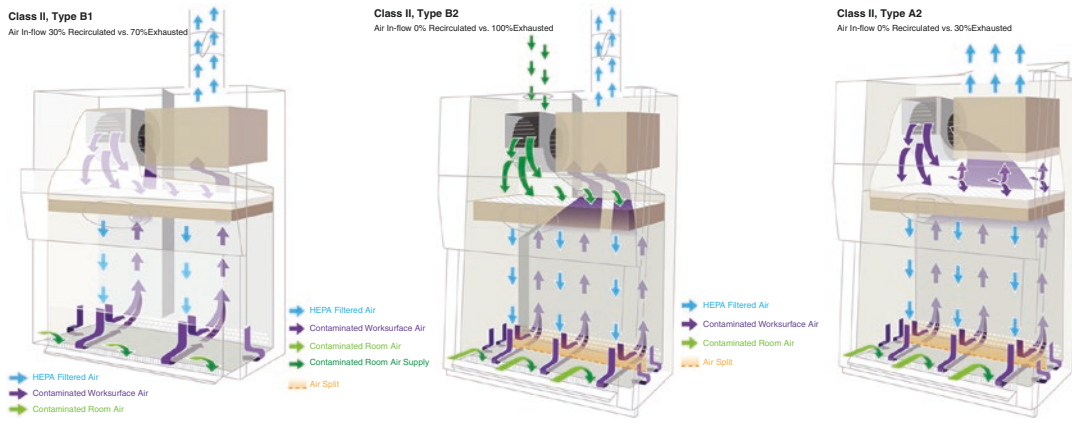


Fig. 3.10 Class II safety cabinet: Air directions and percentage of recirculating and exhausted air for type A2, B1, and B2. (NuAire, Inc., USA., with permission)

appropriate for volatile radionuclides such as radionuclide (I-131). Exhausted air will be discharged to external environment through HEPA filters. Nuclear medicine facilities should consider the total exhaust cabinets for installation [24]. As stated by IAEA, all radiopharmaceutical-labeling procedures, preparation, and elution of ^{99}Mo/^{99m}Tc generator should be executed in class II safety cabinet or isolator [23].

Class III safety cabinet/isolators is a totally enclosed cabinet usually designed to be metal-welded construction and gas tight. Manipulation of samples and work to be done through a gloves port installed at the cabinet front side. Materials are usually loaded from small airlock or pass through box to avoid cross contamination from external environment and to maintain particle count and microbial contamination within the recommended specifications. The cabinet is continuously under negative pressure relative to the ambient room pressure. The air supply is HEPA filtered and could exhaust into laboratory if no toxic chemicals are associated with microbiological process, otherwise it has to be connected to the external environment through a dedicated duct, and the exhaust should be HEPA filtered [23]. This type of cabinets can be used for RBCs labeling.

3.4.2 High-Performance Liquid Chromatography (HPLC)

High-performance/pressure liquid chromatography (HPLC) is a specific form of chromatography for chemical compounds and molecule separation, identification, and quantification [25]. These processes can be performed using analytical HPLC; however, preparative HPLC has different approach for isolation and purification mechanism required for certain radiopharmaceuticals production setup. Analytical HPLC is the most widely used separation method applied to broad spectrum of organic and inorganic, polar and nonpolar, and ionic compounds but is not appropriate for volatile molecules. Figure 3.11 represents HPLC component [26]. It is being used in different fields including industrial, clini-

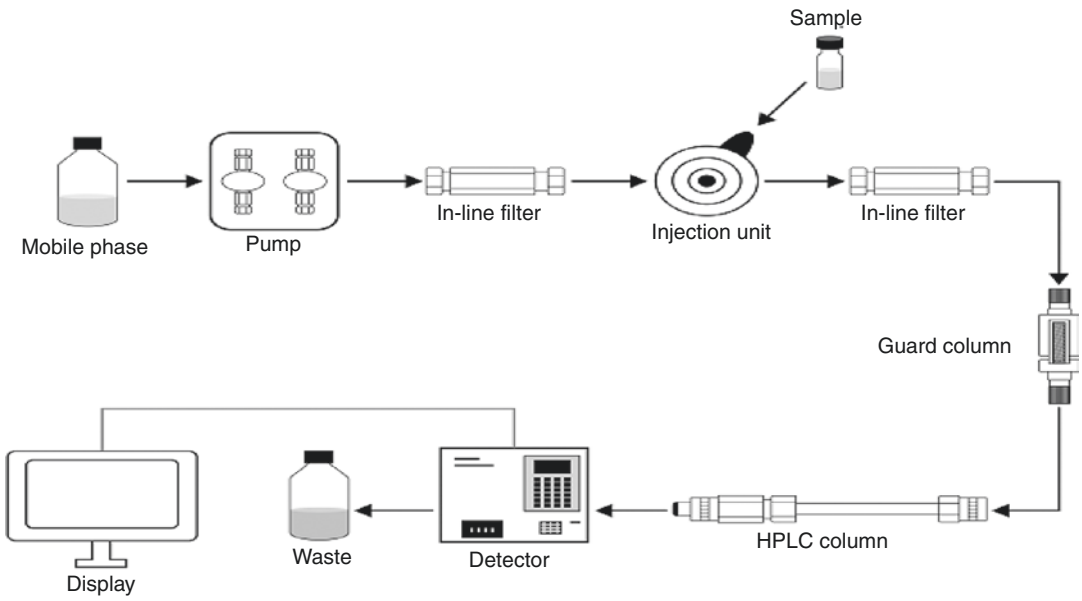


Fig. 3.11 HPLC system components. The pump that allows the flow of the mobile phase with a specified flow rate (mL/min). Injector or injection valve to load the sample into the stream of the mobile phase passing through guard column which acts as a protector of analytical column. The column contains a packing material known as stationary phase which is required for the separation. The detector to identify the eluted compound, and the result is displayed as a chromatogram in PC connected to the HPLC system [26]

cal, environmental, and pharmaceutical applications, providing sensitive and accurate results.

The main concept of separation is based on the interaction between sample (analytes) with stationary phase (column) and mobile phase. The HPLC core component is the separation column that contains the stationary phase, usually it is 5–30 cm in length, loaded with different size of packing materials depending on the application of HPLC. Column length and diameter vary depending on chromatographic procedures [27]. Small size packing molecules require high operational pressure (back pressure) with enhanced system resolution. The packing material or stationary phase vary according to HPLC type.

Silica gel such as silica dioxide, polymer gel (polystyrene and poly methyl acrylate) and other gel including natural material cellulose and agarose are used as stationary phase [28]. The main function of the column is molecule separation depending on their retention time.

The retention time is molecule specific and defined as the time required for the sample to migrate from injection site (t_0) to end of column t_R (detector) or in other words is the time from sample injection to detection.

Several column packing designs are available to adapt various HPLC applications among these porous, non-porous, superficially porous, perfusion, and monoliths packings. HPLC pump is one of the essential HPLC components, and its main function is to push the mobile phase through the analytical column. The pump has to supply constant and pulse-free flow of mobile phase. The composition of mobile phase could be either constant composition (isocratic) or gradient, which means different compositions of mobile phase over time. The gradient compositions created by means of quaternary pump which provides different solvent composition percentage during the run time or analysis.

Furthermore, HPLC detector is a fundamental component of HPLC system. In early HPLC systems, an offline detector was the only method available for sample analysis by collecting fractions of sample under investigation for detection. In 1960s, the first ultraviolet detector was implemented in HPLC systems [29]. Further improvements in detectors started to be developed and implemented such as variable wavelength and diode array detectors. Consequently, many HPLC detectors have been developed and shown potential improvement in a wide range of general and specific HPLC applications [29, 30].

HPLC detector reproducibility and predictability are potential specifications in detector selection. Recently, ultra-high-performance liquid chromatography (UHPLC) requires faster response of detector and contribution of flow cell as the particle size of packing material is sub 2 μm. Desired detector characteristics and specifications for proper HPLC column are listed herein [29, 31, 32]:

- High sensitivity, reproducibility, and predictable response
- Respond to all solutes or have predictable specificity
- Wide linear dynamic range; response that increases linearly with the amount of solute
- Response unaffected by changes in temperature and mobile phase flow
- Respond independently of the mobile phase
- Not contribute to extra-column band broadening
- Provide qualitative and quantitative information on the detected peak
- Chemical nature of analytes and potential interferences
- Limit of detection/quantitation required

There are several types of detectors that could be employed by HPLC system, among these which is widely used in radiopharmaceuticals quality control applications are UV, refractive index, and high-sensitivity radioactive detector [33, 34]. The main purpose of the detector is to measure the concentration of the solute in eluate (i.e., concentration of chemical identities) and concentration of radioactive tracers by chemical and radioactive detectors, respectively [34]. Radiometric detector installed in HPLC system for radiopharmaceuticals quality control is usually made of NaI(Tl) or BGO scintillators to quantify radiochemical purity [34, 35]. Comparing the retention time of the compound

under investigation with cold standard allows the radiochemical identification of the molecule. Other HPLC detector (UV, EC, RI, etc.) is connected in series with radiodetector to identify the radiochemical identity and identify the chemical impurities quantitatively.

Bearing in mind the compatibility of column and detector to HPLC application, HPLC is classified into several types based on the phase system (i.e., stationary phase). The main HPLC types commonly used in radiopharmaceuticals applications are [35]:

- Normal phase chromatography (NP-HPLC)
- Reversed phase chromatography (RP-HPLC)
- Ion-exchange chromatography

In normal phase chromatography or normal phase HPLC (NP-HPLC), the separation process is based on polarity. Polar stationary phase is mostly silica and nonpolar mobile phase such as hexane and diethyl ether [25, 33]. Nonpolar sample will be retained on the column and analyzed. Reverse phase HPLC (RP-HPLC) is another HPLC type where the stationary phase is nonpolar of hydrophobic and polar mobile phase. In this type, the analysis is based on the hydrophobic interactions between a polar mobile phase, the relatively nonpolar analyte, and the nonpolar stationary phase. The analyte retention is proportional to the contact surface area around the nonpolar part of the analyte molecule upon association with the ligand in the aqueous eluent [25].

Ion-exchange chromatography is among those HPLC types. The stationary phase has ionic properties opposite to mobile phase, and the retention is based on the attraction between solute ions and charged sites of the stationary phase. However, the mobile phase will be used in aqueous buffer to control pH and ionic strength [35]. The applications of this type are in ion-exchange chromatography of proteins, high-pH anion-exchange chromatography of carbohydrates, and oligosaccharides and others [25].

Radiochemical identity of radiopharmaceuticals depends on the selection of HPLC type. Analytical column and detector selection must be compatible with chemical properties of evaluated pharmaceutical for proper detection and quantification. The most widely used positron emitters and radiopharmaceuticals 2-[^{18}F]fluoro-deoxy-D-glucose ([^{18}F]FDG) require strongly basic anion-exchange column, pulsed amperometric detector, and radiometric detector [36, 37]. Sodium fluoride [^{18}F]NaF radiochemical purity and identity are evaluated by HPLC equipped by UV detector, radiometric detector, and anion exchange column [36, 38]. Other radiopharmaceuticals such as ^{68}Ga peptide requires reverse phase column, UV, and radiometer detector [39, 40].

HPLC system has a potential in radiopharmacy quality control procedures of finished product to evaluate and quantify the radiochemical and radionuclidic purities to assure the compliance of the final product with guidelines and recommendations.

3.4.3 TLC Scanners

Thin layer chromatography (TLC) and high-performance thin layer chromatography (HPTLC) are known as planer chromatography (Fig. 3.12). Like other chromatography techniques, TLC procedure is applied to separate a mixture of molecules based on their polarity. Polar stationary phase is silica packed as thin layer on glass plate, polyester or aluminum sheet, and proper solvent or solvent mixture as mobile phase. The sample is applied on the stationary phase before immersion in a mobile phase for migration. The movement of mobile phase through stationary phase is called development step [41]. Once the development is completed as the mobile phase reaches front sample point, the detection step will start on the stationary phase. The data are then recorded with TLC scanner equipped with a radiation detector, and the readout is plotted against separation time. The recorded plot is called densitogram [41] (see Chap. 6 for further details).

The main part of the scanner is to serve as radiation detector which could be NaI/PMT, plastic scintillator/PMT, well-type NaI/PMT, and pin diode detectors. To reduce background counts,

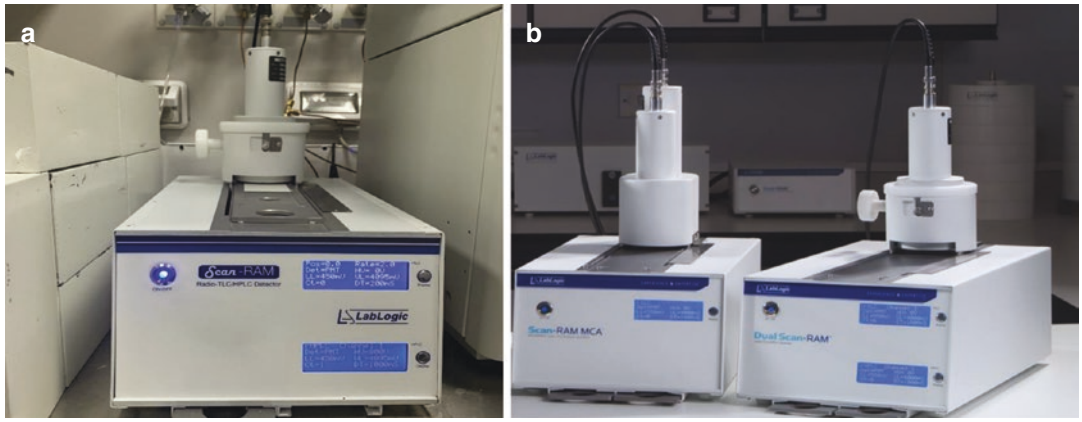


Fig. 3.12 TLC scanner. Commercially available TLC scanners to evaluate the radiochemical purity with thin-layer chromatography in most nuclear medicine laboratories and cyclotron facilities to meet GMP standards. Advanced TLC is combined with MCA to execute basic gamma spectroscopy or radio-nuclidic identity. (**a**) Lateral view of *Lablogic* radio TLC scanner and (**b**) dual TLC and MCA. (LabLogic systems Ltd, UK, with permission)

the detector should be positioned in lead shield or collimator. Either movable detector or collimator set will move over TLC plate, or fixed detector and movable plate both can be seen according to the manufacturer design. The scan time range is normally 1–2 min according to the amount of radioactivity to be detected and user setting.

3.4.4 Gas Chromatography (GC)

Gas chromatography is used analytically to separate compounds that can be vaporized without dissociation. Gas chromatography is known as gas liquid chromatography in which the sample is injected into the column top at certain temperature to allow vaporization. The mobile phase (evaporated sample) is then passed through the stationary phase (column) by the flow of carrier gas, either inert gas such as helium and argon or nonreactive gas such as nitrogen. Column temperature is raised up, maintained, and controlled by oven where the column is located.

GC column is either packed or capillary column depending on the manufacture design. In packed column, the glass or metal tube of the column is filled with fine spherical support. The liquid stationary phase is adsorbed as a thin layer on the surface of these small particles. Capillary column walls are coated with thin layer of liquid stationary phase and referred as open tubular column [35].

The separation of molecules is affected by hold-up time and interaction of those molecules with stationary phase. Hold-up time is defined as the time required by solute to transfer through the column. The molecule functional group will control the interaction between stationary phase and the molecule. As the retention time is elapsed, sample concentration is determined by GC detector and represented in software for calculation from area under peak. Several GC detectors are available such as flame ionization detector (FID), nitrogen phosphors detectors (NPD), electron capture detector (ECD), thermal conductivity detector (TCD), and others [42].

FID is the widely used detector in GC applications. A schematic diagram is shown in Fig. 3.13. In radiopharmaceutical preparation, it is a must to quantify the residual solvents in the finished product as indicated in pharmaceuticals monograph of the European pharmacopeia and the United States pharmacopeia (USP). Quality control of the finished product applying GC analytical method is essential for residual solvent identification and quantification.

3.4.5 Gamma Spectrometers

Gamma spectrometer is a potential tool in radiopharmaceutical industry for radionuclide identification and generating a specific radionuclide

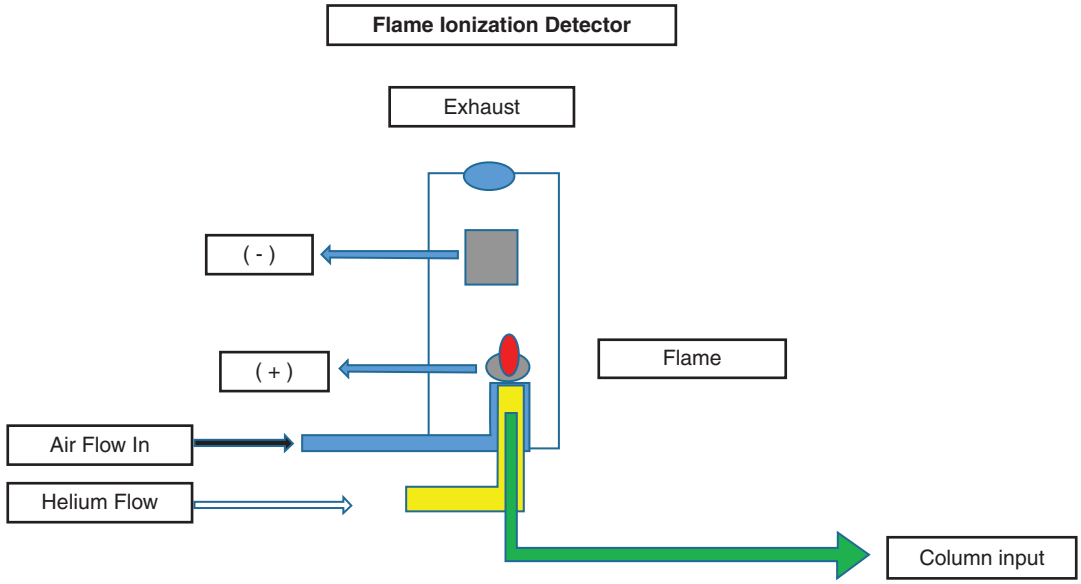


Fig. 3.13 Flame ionization detector (FID). The detector consists of small-volume chamber where the gas chromatograph column is fixed, the sample and carrier gas pass from the column through a hydrogen–air flame. The current produced from burned organic molecules is being measured by electrometer located near to the flame

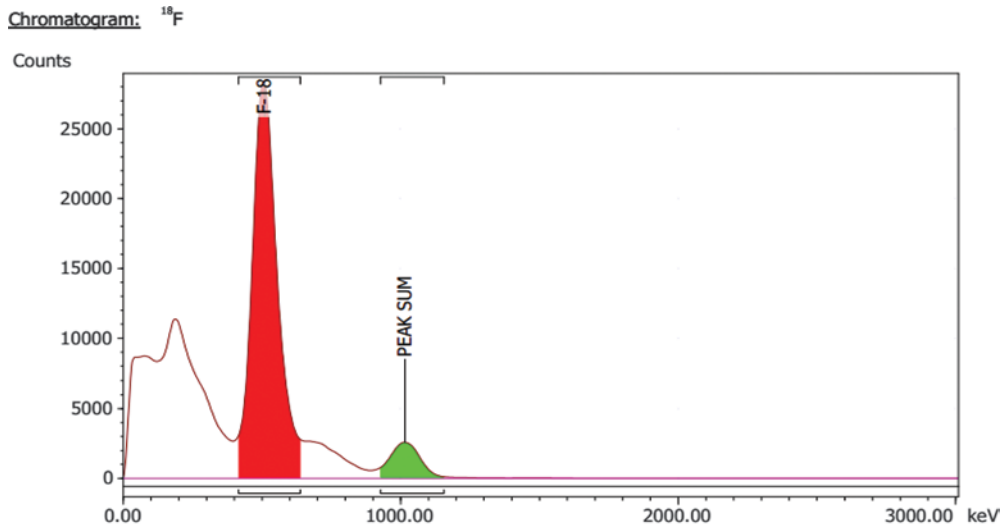
spectrum. Furthermore, detection of radionuclide impurities is associated with the target radionuclide of the finished product. Moreover, it enables determining the percentage of those radionuclide impurities as well as the produced radionuclide [35]. In 1950s, the first gamma spectrometry was done by small and portable NaI(TI) spectrometer. Physical properties of NaI detectors such as good light yield and linearity response make it the most widely used gamma spectrometer [43]. However, other scintillator detectors could be used for this purpose. The semiconductor high-purity germanium (HPGe) detectors make a breakthrough in gamma spectrometry because of their high-energy resolution in the range of 0.5–2 keV [44]. Although HPGe provides the most accurate and precise method for radionuclide purity, the cooling required for the operation of HPGe to maintain the proper functionality is one of the drawbacks.

Gamma spectrometers are classified into two classes, single-channel analyzer (SCA) and multichannel analyzer (MCA) in which energy deposited on the detector is proportional to the interacted gamma rays [13]. Detector size, shape, performance, packing configuration, and intended use of spectrometer are among the most important specifications to verify intended use requirements. The application of gamma spectrometer is a potential factor to define the tradeoff between detector efficiency and energy resolution.

Radionuclidic purity is an important measure to be evaluated in radiopharmaceutical quality control program to quantify radioactive impurities and particular isotopes. Radionuclide purity is defined as the ratio between the desired isotope and the total activity in the compound. In gamma ray spectrum, it is measured as the total count of desired peak in relative to other radioactive peaks. Figure 3.14 illustrates gamma spectrum of ^{18}F. Other equipment are also necessary in radiopharmacy laboratory to ensure other qualities of the finished product for intravenous injection including pH and endotoxins measurements.

3.4.6 pH Meter

A pH meter indicates hydrogen ion concentration of the solution which reflects the solution acidity or alkaline properties. The main part of pH meter is the probe or electrode which could be either



Regions: ^{18}F Detector: Osprey

Name	Start (keV)	End (keV)	Centroid (keV)
F-18	414.85	638.46	511.95
PEAK SUM	926.80	1156.29	1018.01
2 Peaks			

Fig. 3.14 Gamma spectrum of ^{18}F-FDG. The evaluation of radionuclidic purity during the quality control of FDG by multi-channel analyzer showing the ^{18}F peak at 511 keV and sum peak at 1022 keV

glass electrode or ion selective field effective transistor (ISFET) connected to electronic display for pH reading purposes [45]. The glass electrode is most widely used in pharmaceutical applications. The system consists of measuring electrode and reference electrode. The former provides voltage in mV proportional to hydrogen ion concentration while the latter provides a constant potential regardless the pH of the solution. The measuring electrode is usually immersed in a high-acidity reference solution such as the normally used 0.1 N HCl, and reference electrode is typically Ag/AgCl salt that surrounds the wire electrode [45]. The pH electrode components and configuration are shown in Fig. 3.15.

Daily calibration of pH meter with standard buffer solutions of known pH is required before measuring unknown samples. Radiopharmaceutical GMP require the daily calibration of pH meter with reference buffer of pH 4, 7, and 10. Microelectrode is commercially available to measure the sample of volume 10 μL [36].

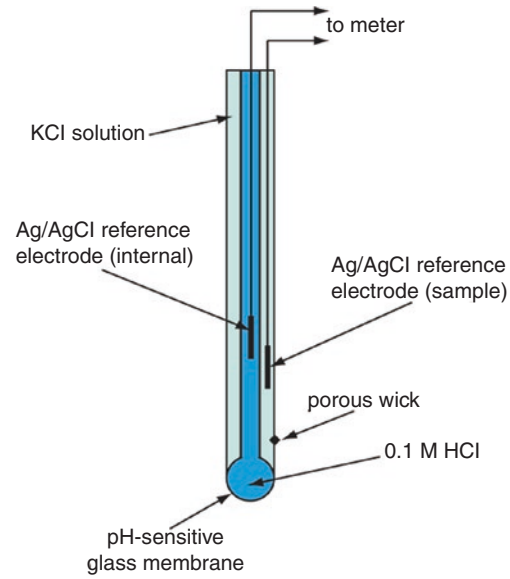


Fig. 3.15 pH meter basic components of glass electrode. The measuring electrode is bulb made of porous glass or preamble glass membrane coated with metal salts or silica and filled with high acidity solution. External reference electrode is surrounded by saturated KCl

Fig. 3.16 The Charles River Endosafe®-PTS™ System, an FDA-approved endotoxin system. A point-of-use and rapid portable system that provides quantitative LAL results in a quick fashion. It employs LAL reagents in a disposable test cartridge shown on the right. (Images credit of *Charles River Laboratories*, Inc., USA, with permission)

3.4.7 Endosafe PTS

Bacterial endotoxin should be assessed and evaluated before the product release for IV injection. Endotoxin is lipopolysaccharides found in the membrane of gram-negative bacteria. Endotoxin test is used to quantify the limulus ambocyte lysate (LAL). The test method could be gel clotting technique, turbidity approach, or chromogenic method. Gel clotting based on adding equal amount of sample and LAL reagent, and the mixture is incubated for 1 h at 37 °C. After incubation time, the tube will be inverted if any clot formation indicates that the presence of endotoxin. This approach cannot provide any quantification regarding the endotoxin amount. Turbid metric technique provides quantification of endotoxin determined by the change of sample color as a result of endotoxin reaction with LAL reagent. The amount of turbidity increases with time based on the endotoxin concentration in the solution. The standard curve is plotted, as time versus endotoxin concentration in endotoxin unit (EU) or international unit (IU) per milliliter. Endotoxin concentration is determined from the standard curve based on the reaction time of the sample. Chromogenic method is based on using substrate which releases chromophore as a result of interaction with endotoxin. The amount of chromophore is proportional with the endotoxin level existing in the sample. This method applies predefined end point. Charles River Laboratories has developed the Endosafe PTS™, shown in Fig. 3.16, which is a rapid portable device that determines quantitatively endotoxin concentration (EU) within 15 min through their unique cartridge technology.

3.5 Conclusion

Nuclear medicine procedures involve administration of radiopharmaceuticals into humans and thus quality of both imaging and non-imaging equipment as well as the injected compound must be properly evaluated and monitored. Equipment should be subjected to quality control program with calibrated standard sources. The availability of such radioactive sources for routine testing is important in order to maintain a medical standard of care on a daily basis. In normal radiopharmacy laboratory as well as in cyclotron production facility, a number of tests are requested to ensure com-

pliance with national or international regulations and safety of the injected compounds. Moreover, the quality assurance and control parameters should be well established and documented. This is to be maintained for all imaging, non-imaging, and radiopharmacy toolkits. Implementation of such quality measures using proper methodologies will ensure improvement of diagnostic accuracy and performance of nuclear medicine practices.

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