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Review Article

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Fundamental concepts of radiopharmaceuticals quality controls

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ABSTRACT

Quality control (QC) procedures should always be performed following radiopharmaceutical preparation and prior to patient administration. The main aim of QC is to ensure optimal radiopharmaceutical product properties except for some short half-life tracers such as some positron emission tomography (PET) imaging probs. by dispensing a radiopharmaceutical of the highest quality the risk of having to repeat a nuclear medicine study due to poorly performing radiopharmaceuticals will be reduced. The existence of radiochemical impurity or impurities in radiopharmaceutical cause unnecessary radiation burden to the patient or undesirable high background without adding to the diagnostic information or improving treatment. Therefore, radiopharmaceuticals quality control is crucial and involves two different aspects including pharmaceutical parameters (such as sterility, bacterial endotoxins/ pyrogens, bioaffinity and biodistribution studies) and radioactive parameters (such as radionuclide and radiochemical purity) and chemical impurity which will be focused on here.

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Introduction

A radiopharmaceutical is a radioactive compound which possesses diagnosis and/or therapeutic features for human diseases (1). WHO describes radiopharmaceuticals as unique medicinal formulations containing radioisotopes which are used in major clinical areas for diagnosis and/or therapy (2). In nuclear medicine most of the radiopharmaceuticals are administered for diagnostic purposes, while the rest are therapeutic ones. The majority of radiopharmaceuticals in nuclear medicine are administered to patients as intravenous injections. Since radiopharmaceuticals are intended for administration to humans, they must undergo strict quality control (QC) measures. Basically, quality control involves several specific tests and measurements that ensure the purity, potency, product identity, biologic safety, and efficacy of radiopharmaceuticals (3, 4).

According to the European Pharmacopoeia (EP) and US Pharmacopoeia (USP) all injections must be sterile, apyrogenic, free from extraneous particles and at suitable pH, ionic strength and osmolality. Moreover, radioactive injections should include the correct radiochemical and radionuclidic purity and have the correct radioactivity present at the stated time of injection. To that end, radiopharmaceuticals quality control is crucial and involves two different aspects including pharmaceutical parameters and radioactive parameters (Fig. 1). Pharmaceutical parameters designed to ensure that no microbiological, pyrogenic or particulate contamination can harm patients, while radioactive parameter designed to ensure that the intended radiation exposure of patients is kept to a minimum by confirming that the radioactivity, radiochemical and radionuclidic purity are assured. Quality control procedures should always be performed following radiopharmaceutical preparation and prior to patient administration to ensure optimal radiopharmaceutical product. Some of these QC tests are performed by the manufacturers, while others must be performed by the compounding personnel (4).

The introduction of kits for administration of short-lived radionuclides such as 99mTc and the onsite preparation of many radiopharmaceuticals require that quality control tests be performed during in-house preparations before dispensing these products for human administration. Official requirements for the quality control standards can be found in the manufacturer's package inserts, USP, BP, and Nuclear Regulatory Commission (NRC) regulations (5). In this review our focus is mainly on the QC of ^{99m}Tc labeled radiopharmaceuticals. Therefore, fundamental concepts, definitions and different algorithm of QC will be presented.

A radiopharmaceutical is a radioactive compound which possesses diagnosis and/or therapeutic features for human diseases. Due to the trace amount of administered diagnostic radiopharmaceuticals to humans, they are pharmacologically inactive; this is the most imperative difference between radiopharmaceuticals and other pharmaceuticals. However, some therapeutic radiopharmaceuticals are

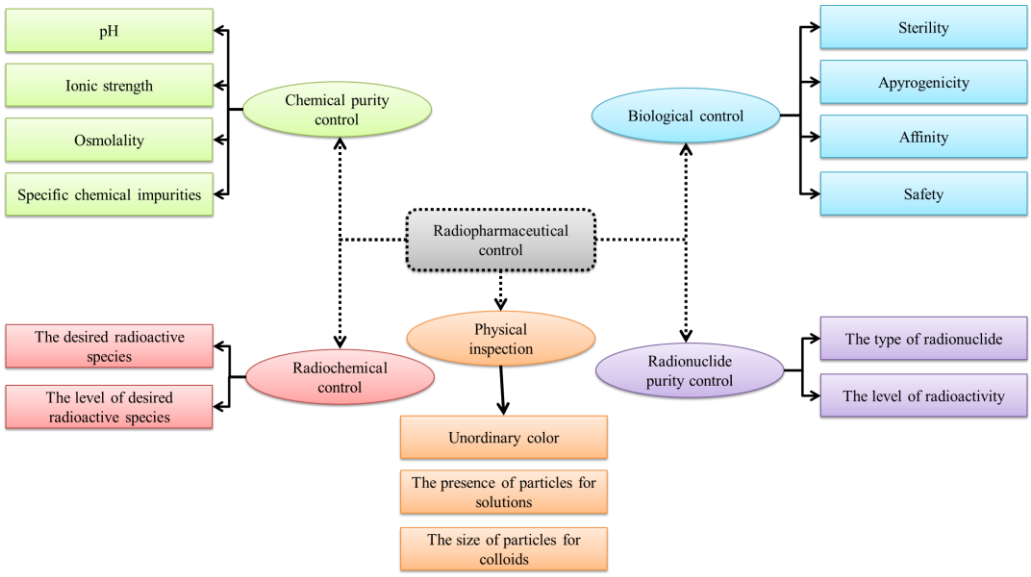

Figure 1 Different aspects of radiopharmaceuticals quality controls

pharmacologically active (6). Like every other chemicals, radiopharmaceuticals can be classified based on their chemical structural characteristics, physiochemical form or their mechanism of action (1). From physiochemical perspective radiopharmaceuticals fall into categories such as simple elements (such as ^{131}I), chemical complexes (such as radiolabeled small molecules, antibodies and peptides), blood cellular elements (such as ^{99m}Tc-labeled RBC) and particles (^{99m}Tc labeled albumin aggregate). This type of categories can provide some information about their QC process; even though the members of a category cannot be manage with the exact same QC process (7). One of the most useful classifications for radiopharmaceuticals is based on their mechanism of action (Table 1). It should be mentioned that some radiopharmaceuticals may act through one or more of these mechanisms (8).

Quality control algorithms

Different aspects of quality control including pharmaceutical parameters and radioactive parameters should be investigated before administration of the radiopharmaceutical to the patient as follow (Fig.1):

- Radionuclide purity control
- Radiochemical purity control
- Chemical purity control
- Biological control
- physical inspection

These parameters will be explained below (9):

Radionuclide purity

Radionuclidic purity is defined as the fraction of the total radioactivity in the form of the desired radionuclide present in a radiopharmaceutical. Impurities originate from undesired nuclear reactions because of isotopic impurities in the target material. The undesirable radionuclides may belong to the same element as the desired radionuclide (such as iodine isotopes in ^{131}I) or to a different element (such as ^{99}Mo in ^{99m}Tc-labeled preparations). The presence of any kind of radiochemical impurity in radiopharmaceutical contributes to unnecessary radiation burden to the patients or undesirable high background without adding to the diagnostic information or improving treatment. These impurities can be removed by appropriate chemical methods. Radionuclidic purity is determined based on the half-lives, the type of emitted radiations and the energy of the radiation (10).

Radionuclides that emit γ-rays are distinguished from one another based on their γ-spectra obtained with a NaI(Tl) or lithium-drifted germanium (Ge(Li)) detector coupled to a multichannel analyzer. Pure β emitters due to weak penetration of this ray are not as easy to check because of the difficulty in counting in a well counter. Using a β spectrometer or a liquid scintillation counter may alleviate this problem. Radionuclidic purity depends on the relative half-lives and the quantities of the desired radionuclide; hence it changes as the time passes by. If small quantities of a long-lived contaminant radionuclide exist in the sample, it is difficult to detect in the presence of large quantities of a desired short-lived radionuclide. Therefore, the short-lived radionuclide must have allowed decaying before the long-lived activity is measured. For example, trace amounts of various

Table 1 Examples of radiopharmaceuticals and their mechanism of action

No.	Radiopharmaceutical	Mechanism of action	Description
1	^{99m}Tc-DTPA	Passive diffusion	Passive diffusion through damaged BBB in brain imaging
2	^{99m}Tc-phosphonate	Ion exchange	Bone imaging through ion exchange with phosphate ion
3	^{99m}Tc-macroaggregated albumin	Capillary blockage	Particles block low percentage of capillaries in the lung for imaging
4	^{99m}Tc-sulfur colloid	Phagocytosis	The reticuloendothelial cells in the liver, spleen, and bone marrow remove particles based on their size
5	^{201}Tl	Active transport	Uptake in the myocardium through Na^+/K^+ ATP-ase pump
6	heat-damaged ^{99m}Tc-RBC	Cell sequestration	Spleen cleans up damaged RBC
7	^{18}F-FDG	Metabolism	Uptake in myocardial, brain and cancerous tissues
8	^{11}C-dopamine	Receptor binding	^{11}C-dopamine binds to dopamine receptors in the brain
9	^{99m}Tc-RBC	Compartmental localization	Blood pool study for example internal bleeding in gastrointestinal reign
10	radiolabeled antibodies	Antigen–antibody complex formation	Localize tumors in cancer disease
11	^{111}In-labeled leukocytes	Chemotaxis	Imaging infection

radionuclidic impurities in the ^{99m}Tc-eluate can be measured by a Ge(Li) detector after ^{99m}Tc fully decayed (11). In the real world achieving a 100% pure radionuclide is very hard if not possible; hence for different radionuclides a certain amount of contamination is accented (Table 2).

Radiochemical purity (RCP)

The radiochemical purity of a radiopharmaceutical is the fraction of the total radioactivity in the desired chemical form in the radiopharmaceutical (Table 3). Radiochemical impurities have various reasons including decomposition due to the action of solvent, change in temperature or pH, light, presence of oxidizing or reducing agents, incomplete reaction, and radiolysis. For example free $^{99m}TcO_4$ and hydrolyzed ^{99m}Tc in ^{99m}Tc-labeled complexes (complexes of ^{99m}Tc with co-ligand or transfer ligand) are the main radiochemical impurities for ^{99m}Tc-based radiopharmaceuticals (7).

The presence of radiochemical impurities in a radiopharmaceutical reduces quality of imaging due to the high background radiation from the surrounding tissues and blood, and gives unnecessary radiation burden to the patient. The specific activity of the radioactive material, the type and energy of the emitted radiation and the half-life of the radionuclide contribute to radiochemical impurities. Having that said absorption of radiations by labeled molecules results in the formation of free radicals with unpaired electrons, which are chemically active species and decompose other molecules through chemical reactions. Furthermore, free radicals are capable to decompose water and produce H_2O_2 or HO_2^- which can react with labeled molecules. Particles such as β and α are more damaging than γ-rays due to their short range and complete local absorption in matter (high LET) (Table 3). The stability of a compound is time-dependent on exposure to light, change in temperature, and radiolysis (due to radiation). The longer a compound is exposed to these conditions,

Table 2 Examples of required radionuclidic purity for commonly used radionuclides

No.	Radionuclide	Contaminants	Acceptable limits of contaminants	Ref.
1	^{99m}Tc	^{99}Mo	Less than 0.15 μCi per 1 mCi of ^{99m}Tc	(12)
2	^{111}In	^{110m}In	Each of them less than 3 μCi per 1 mCi of ^{111}In	(13)
		^{114m}In		
3	^{201}Tl	^{200}Tl	Less than 2% of total activity	(14)
		^{202}Tl	Less than 2.7% of total activity	
		^{203}Pb	Less than 0.3% of total activity	

Table 3 Examples of required radiochemical purity for commonly used radiopharmaceuticals

No.	Radiopharmaceutical	Acceptable RCP	Ref.
1	^{99m}Tc-gluceptate (^{99m}Tc-GH)	90%	(15)
2	^{99m}Tc-medronate (^{99m}Tc-MDP)	90%	(16)
3	^{99m}Tc-sodium pertechnetate (Na$^{99m}TcO_4$)	95%	(4)
4	^{99m}Tc-succimer (^{99m}Tc-DMSA)	85%	(17)
5	^{99m}Tc-arcitumomab	95%	(18)
6	^{32}P-sodium phosphate	100%	(19)
7	^{67}Ga-gallium citrate	97%	(20)

the more it tends to decompose; hence, most radiopharmaceuticals cannot be administered after their assigned expiration date. Substances with anti-oxidant features such as sodium ascorbate, ascorbic acid, and sodium sulfite are often added to maintain the stability of radiopharmaceuticals under the mentioned conditions (21).

A number of analytical methods are used to detect and determine the radiochemical impurities in a given radiopharmaceutical. Some of these methods are precipitation, paper, thin-layer, and gel chromatography, paper and gel electrophoresis, ion exchange, solvent extraction, high performance liquid chromatography, and distillation. These methods are briefly outlined below.

Paper and thin layer chromatography

In these methods a small drop of the radiopharmaceutical is put onto the bottom of a strip of support medium (e.g. paper, silica gel coated sheets). The strip is put into a tank containing a small amount of solvent. The solvent migrates up the strip due to the capillarity effect. The components of the radiopharmaceutical are separated according to the solubility in the solvent and adsorption to the support medium (Fig. 2). Detection of the radioactivity in the strip can be carried out in a number of ways (9, 22).

a) The simplest method is to cut the strip and count the activity in the sections in a radionuclide calibrator or a well scintillation counter (Fig. 2b). The percentage of activity in each section can then be determined. For example, if two solvent systems (saline and methanol) are applied for a ^{99m}Tc-radiopharmaceutical while saline moves $^{99m}TcO_4$ to the solvent front and methanol moves $^{99m}TcO_4$ and the compound of interest to the solvent front then the calculation in Fig. 2b can be carried out to determine the radiochemical purity. This method does have several limitations including (a) radionuclide

calibrators are inaccurate for samples of low activity due to the lower level of detectability and the accuracy of the calibrator at the lower range setting, and (b) well scintillation counters should be avoided for samples of high activity, as these can exceed the count rate capabilities due to the resolving time of the detection system.

b) The strip can be imaged under a gamma camera. Regions of interest can be drawn around the areas of radioactivity and the percentage of counts in each region can be determined. This method has the advantage of imaging the whole chromatography strip enabling artifacts to be seen, however, it is not practicable for most hospital departments due to the cost of camera time.

c) The strip can be imaged using a radiochromatogram scanner. A radiochromatogram scanner uses a sodium iodide detector to detect the gamma emission (Fig. 2a). If the scanner is linked to an integrator, then quantification of the peaks can be carried out. This equipment is not suitable for counting emissions from some isotopes (for example chromium (^{51}Cr) or iodine (^{125}I)) due to statistics associated with counting low activities (Fig. 2).

d) Analysis of the strip can be performed using storage phosphor imaging. A phosphor screen accumulates a latent image of the distribution of radioactivity on the strip. Scanning the screen with a laser allows the location and intensity of of the strip. Regions of interest can be drawn and integration carried out to determine activity in each region. By varying the time of exposure of the strip to the phosphor screen, radiopharmaceuticals containing many different isotopes, or of different activities, can be analyzed. One of the biggest drawbacks to paper and thin layer chromatography methods of determining RCP is the resolving power of the methods. Most methods commonly used will only resolve one component and so two or three methods may be needed to identify all the major contaminants in a product. Time can also be a limiting factor with some methods taking 20-30 minutes to develop, or even longer.

High Performance Liquid Chromatography (HPLC)

TLC RCP methods may not be sufficient to identify all the compounds which are present in a product. HPLC has a higher sensitivity and resolving power than simple TLC methods. HPLC separation operates on the hydrophilic/lipophilic properties of the components of a sample applied. Gamma emitters are detected using a well scintillation counter connected to a rate meter. Other detectors (UV or refractive index) can be connected in series allowing simultaneous identification of compounds. It is unnecessary to perform HPLC on radiopharmaceuticals reconstituted from licensed cold kits. It is useful to have techniques available for the purpose of eliminating a cause of any abnormal patient scan.

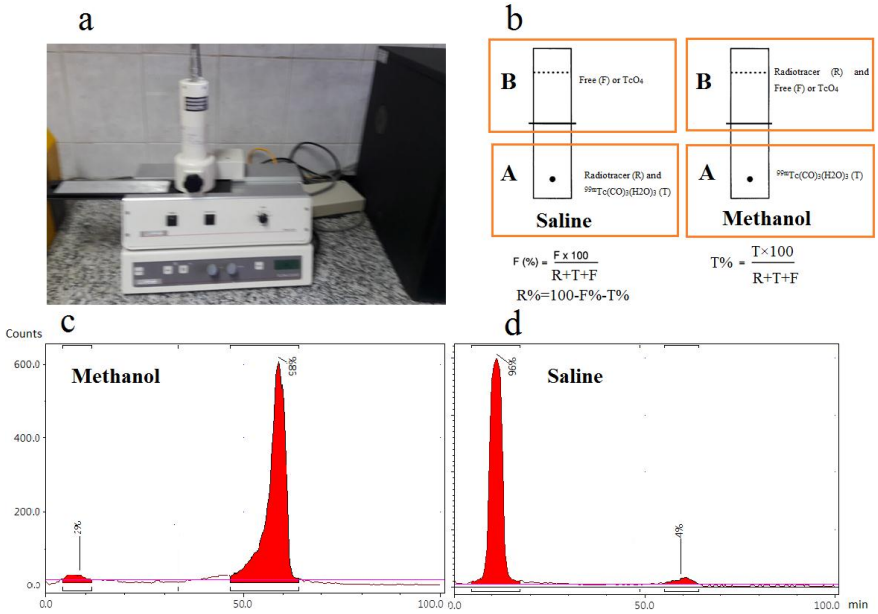

Figure 2 (a) Illustration of a TLC system for analyzing radiochemical purity of ^{99m}Tc labeled radiopharmaceuticals. (b) The representation of calculation equations which will be carried out by the integrator in this case the example belongs to a radiotracer (R) labeled with $^{99m}Tc(CO)_3(H_2O)_3$ (T) using TcO_4(F) as the precursor. The TLC has been performed in two different solvent system including methanol and saline. (c) Methanol moves R and f while T will stay at the starting point. (d) Because in this case R is very lipophilic, saline cannot move R.

For radiopharmaceuticals prepared 'in-house' or novel compounds for research purposes, an HPLC method for estimating radiochemical purity is essential. It should be noted that HPLC does not detect colloidal contaminants and that this should be estimated using TLC methods (Fig. 3) (22-24).

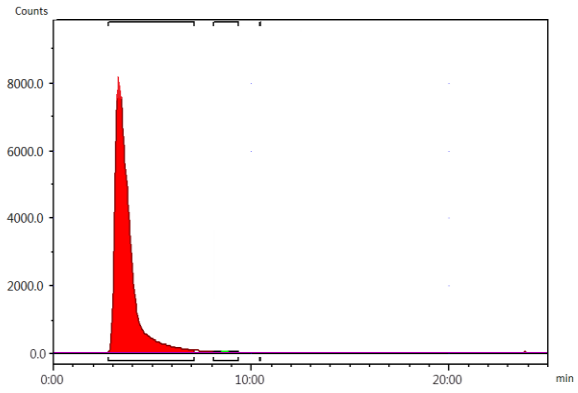

Figure 3 HPLC choromatograme of $^{99m}Tc(CO)_3(H_2O)_3$ which confirms high RCP

Paper or polyacrylamide gel electrophoresis

In order to perform a paper or polyacrylamide gel electrophoresis, a radioactive sample will be placed on a paper or polyacrylamide gel soaked in a suitable buffer, and then a proper voltage will be applied across the paper or gel for a certain period of time. The components of the radioactive sample move to different positions along the paper or gel medium, regarding to their charge and ionic mobility. Afterward the distribution of radioactivity along the strip or gel column can be measured by a counter. It is worth to note that this method is appreciated for large molecules such as proteins. Since overall charge of protein molecules above or below their isoelectric pH (pI) is not neutral, most proteins can be separated by this method with the use of appropriate buffers. For instance, a good separation of free iodide and radioiodinated proteins can be achieved by electrophoresis in buffer (7).

Biodistribution studies

The clinical efficacy of every radiopharmaceutical, before their administration to humans, must be evaluated by testing in animals and gets approved by FDA. Therefore, the biodistribution study of a radiopharmaceutical is crucial in establishing its efficacy and usefulness. This type of study includes tissue distribution, plasma clearance, urinary excretion, and fecal excretion after administration of the radiopharmaceutical. In order to perform a distribution study the radiopharmaceutical is first injected into animals such as mice, rats, and rabbits. After different time intervals the animals are sacrificed and their organs are harvested. The levels of radioactivity in the harvested organs are measured and different calculation and comparison are carried out. This type of information can indicate how good the radiopharmaceutical is for imaging of the interested organ.

In the next step human biodistribution data can be obtained by gamma camera imaging. These types of data include the rate of localization of a radiopharmaceutical in an organ which is related to its rate of plasma clearance after administration. The time that is needed in order to initial plasma activity drop by half is defined as halftime of a radiopharmaceutical. This parameter can be calculated by collecting serial samples of blood at different time intervals after injection and plotting activity versus time. Urinary and fecal excretions of a radiopharmaceutical are important as well because faster the urinary or fecal excretion is equal to less the radiation exposure. Urinary and fecal excretions values also can be determined by sampling the urine or feces at specific time intervals after administration of the sample. The examination of other parameters such as toxic effects of radiopharmaceuticals, damage to the tissues, physiologic dysfunction of organs, and even the death of the species should be performed (25-27).

Specific chemical impurity

The fraction of the material in the desired chemical form is called the chemical purity of a radiopharmaceutical. Chemical impurities originate in different areas including the breakdown of the material either before or after labeling, the inadvertent addition during labeling, and the undue accompaniment in the preparation of the compound. For example, aluminum is a chemical impurity in the ^{99m}Tc-eluate and can cause serious problems including toxicity. The presence of a slight amount of globulins in the preparation of albumin aggregates can be considered as chemical impurity. It is noteworthy that additives, acid, alkali, and buffers are not considered impurities. The presence of chemical impurities before radiolabeling may lead to undesirable labeled species that contribute to adverse effect on diagnostic test. To that end, purification of radiopharmaceuticals from these impurities is unavoidable and often carried out by methods of chemical separation such as precipitation, solvent extraction, ion exchange, and distillation (28).

Sterility tests

Sterility testing is performed to prove that radiopharmaceuticals are highly free of viable microorganisms including fungi and bacteria. These tests must be performed aseptically so that external contaminations unable interfere to the test samples during the experiment. A sterile laminar-flow hood and well trained personnel for performing these tests are preferable. USP 32 indicates sterility tests are performed by incubating the radiopharmaceutical sample in two different ways in order to detect bacterial and fungal contaminations:

1: For bacterial contaminations the radiopharmaceutical sample should be incubated in fluid thioglycollate medium at 30–35 °C for 14 days
2: For fungal contaminations the radiopharmaceutical sample should be incubated in soybean–casein digest medium for incubation at 20–25 °C for 14 days
The sample volume for the test should be at least as great as that for a human dosage. If bacterial growth is observed in either test, the radiopharmaceutical is not sterile. The most prominent drawback for radiopharmaceutical sterility test is that sterility testing frequently takes longer than the half-lives of many common short-lived radionuclides such as ^{99m}Tc. In these cases, the product of interest is released for human use provided the manufacturer has already established its sterility and apyrogenicity at the production level.
In order to resolve this major drawback, some *in vitro* sterility tests took advantage of radioassay of $^{14}CO_2$ formed by the metabolism of microorganisms as they are using ^{14}C-glucose in culturing medium. The basic principle of the test involves the addition of the test sample to a trypticase soybroth culture medium containing ^{14}C-glucose. In this method collection of $^{14}CO_2$ gas indicates the presence of both aerobic and anaerobic microorganisms. Radioassay is done with a gas ionization chamber and can be detected by this method. The bold feature of this method is that it requires only a short amount of time, about 3–24 h, compared to many days in other methods approved by the USP (29).

Pyrogenicity tests

All radiopharmaceuticals for human administration are required to be pyrogen free. Pyrogens are either polysaccharides or proteins produced by the metabolism of microorganisms. Even though the bold examples of pyrogens are bacterial endotoxins (BE), various chemicals can add pyrogens to a radiopharmaceutical solution. It is noteworthy that sterility of a solution does not guarantee its apyrogenicity and sterilization process does not destroy the pyrogens in a radiopharmaceutical. There is no specific method for making a sample apyrogenic, hence the necessary precautions should be taken from the beginning. Pyrogens essentially originate from the metabolism of bacteria; hence, the best way to prevent pyrogenic contamination is to use sterile glassware, solutions, and equipment under aseptic conditions in any preparation procedure.
In order to assess apyrogenicity of radiopharmaceuticals USP Rabbit test and Limulus Amebocyte Lysate (LAL) test can be carried out. For rabbit test, three mature normal rabbits weighing not less than 1.5 kg are chosen for the test, and their temperatures are controlled by keeping them in an area of uniform temperature. The volume of the test sample must be an equivalent human dosage, on a weight basis, and often three to ten times the human dosage by volume is used to achieve a greater safety factor. The test sample is injected into the ear vein of each of the three rabbits. The rectal temperatures of the animals are measured 1, 2, and 3 h after injection of the test material. If the rise in temperature in individual animals is less than 0.6 °C and if the sum of the temperature rises in all three animals does not exceed 1.4 °C, then the test sample is considered apyrogenic. If any of the above conditions is not fulfilled, the test must be repeated with five more rabbits. If not more than three of the total eight animals show a temperature rise of 0.6 °C or more individually and if the sum of the individual temperature rises does not exceed 3.7 °C, the material is considered pyrogen free (30).
A rapid method for bacterial endotoxin test, also called the LAL test, is employed for the detection and quantitation of endotoxin-type pyrogens. This method uses the lysate of amebocytes from the blood of the horseshoe crab, Limulus polyphemus. The principle of the test is based on the formation of an opaque gel by pyrogens in the presence of Ca^{2+} upon incubating the sample with the LAL at 37 °C. An assay mixture usually consists of 0.1 mL LAL and a test sample at pH 6–8. The reaction takes place within 15–60 min after mixing and depends on the concentration of pyrogens. The formation of a gel indicates the presence of pyrogens. The LAL test is conducted on unknown samples as well as on E. coli endotoxin and water samples. Usually 0.1 mL of each sample and LAL are incubated at 37 °C for 60 min. If the E. coli endotoxin sample shows gel formation (positive control) and the water sample shows no gel formation (negative control), then unknown samples are considered positive or negative depending on whether they form gel or not. The US FDA has approved the LAL test for endotoxin-type pyrogens (30, 31).

Conclusion

Since radiopharmaceuticals are intended for administration to humans, it is imperative that they undergo strict quality control measures. Basically, quality control involves several specific tests and measurements that ensure the purity, potency, product identity, biologic safety, and efficacy of radiopharmaceuticals. All quality control procedures that are applied to nonradioactive pharmaceuticals are equally applicable to radiopharmaceuticals; in addition, tests for radionuclidic and radiochemical purity have to be carried out. Often these quality control tests are carried out by the manufacturers from the beginning of production all the way up to the finished product. However, the introduction of kits, the increasing use of short-lived radionuclides such as ^{99m}Tc and the onsite preparation of many radiopharmaceuticals demand on site quality control. The quality control tests fall into two categories: physicochemical tests and biological tests. The physicochemical tests indicate the level of radionuclidic and radiochemical impurities and determine the pH, ionic strength, osmolality, and physical state of the sample. All of these parameters have to be in a certain range according to USP or EP. For example the level of radionuclide purity, radiochemical purity and chemical

impurities for every radiopharmaceutical have been determined. It is noteworthy that the biological tests to establish the sterility, apyrogenicity, and toxicity of the material are crucial. In order to provide sterility for a radiopharmaceutical the product should be produce in aseptic condition or applying one of the known procedures to reach sterility (usually filtration). On the contrary one a product is not pyrogens free, there is no way to make it apyrogen and it should be discarded.

Conflicts of interest

The authors declared no conflict of interest.

Acknowledgement

The authors declared non.

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