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REVIEW ARTICLE / DERLEME MAKALE

QUALITY ASSURANCE AND QUALITY CONTROL OF RADIOPHARMACEUTICALS: AN OVERVIEW

RADYOFARMASÖTİKLERİN KALİTE GÜVENCESİ VE KALİTE KONTROLÜ: GENEL BİR BAKIŞ

Meliha EKİNCİ[1], Ralph SANTOS-OLİVEİRA[2,3], Derya İLEM-ÖZDEMİR[1*]

[1]Ege University, Faculty of Pharmacy, Department of Radiopharmacy, 35040, Izmir, Turkey

[2]Brazilian Nuclear Energy Commission, Nuclear Engineering Institute, Laboratory of Synthesis of Novel Radiopharmaceuticals and Nanoradiopharmacy, Rio de Janeiro, 21941906, Brazil

[3]Zona Oeste State University, Laboratory of Nanoradiopharmaceuticals and Radiopharmacy, Rio de Janeiro, 23070200, Brazil

ABSTRACT

Objective: *Radiopharmacy is a special field of pharmacy that examines, develops, conducts quality controls, deals with distribution and application of pharmaceutical forms called radiopharmaceuticals that are used for diagnostic and therapeutic purposes, carrying pharmaceutical and radioactive properties together. Radiopharmaceuticals contain radionuclides. This is the most important difference that distinguishes radiopharmaceuticals from other conventional drugs. Since radiopharmaceuticals are administered to humans, they must be sterile, pyrogen-free, isotonic, isohydric, and subject to all quality control tests required for conventional drug. Also, additional quality control tests are required due to radionuclide they contain. In this review, quality control tests applied to radiopharmaceuticals, hospital radiopharmacy laboratory types and Good Radiopharmacy Practices (GRP) will be discussed.*

Result and Discussion: *Radiopharmaceuticals should be prepared in accordance with standards specified in relevant sections of pharmacopoeias. For each series of radiopharmaceuticals, tests prescribed in the pharmacopoeias and records must be kept. Production and preparation of radiopharmaceuticals should be carried out in accordance with Good Manufacturing Practices for sterile preparations and GRP for radioactive products. However, radiopharmaceuticals that pass quality control tests can be administered to patients after dose measurements are made in dose calibrators. Thus, the patient's safety and benefit are maximized, while the risk is minimized. Some radiopharmaceuticals with a short half-life are used before quality control tests are completed. In this case, the effectiveness and continuation of the quality assurance system should be tested at*

* **Corresponding Author / Sorumlu Yazar:** Derya İlem-Özdemir
e-mail / e-posta: deryailem@gmail.com, **Phone / Tel.:** +902323111963

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appropriate intervals. According to procedures performed by hospital radiopharmacy laboratories, international standards are determined as Level IA/B, Level IIA/B and Level IIIA/B/C. Quality assurance of radiopharmaceuticals is provided by a sufficient number of trained personnel within the scope of GRP, devices that have been calibrated and controlled, appropriate substances and a working order in which tests determined at each stage are made and results are recorded accurately and regularly.

Keywords: *Good radiopharmacy practices, radiopharmaceuticals, radiopharmacy lab, quality assurance, quality control*

ÖZ

Amaç: *Radyofarmasi, radyofarmasötik adı verilen, teşhis ve tedavi amaçlı kullanılan, farmasötik ve radyoaktif özellikleri bir arada taşıyan farmasötik formları inceleyen, geliştiren, kalite kontrollerini yapan, dağıtımı ve uygulaması ile uğraşan özel bir eczacılık alanıdır. Radyofarmasötikleri diğer konvansiyonel ilaçlardan ayıran en önemli fark; radyofarmasötiklerin radyonüklid içermesidir. Radyofarmasötikler insanlara uygulandığı için steril, pirojensiz, izotonik, izohidrik olmalı ve geleneksel ilaç için gerekli tüm kalite kontrol testlerine tabi olmalıdır. Ayrıca içerdikleri radyonüklid nedeniyle ek kalite kontrol testlerinin uygulanması da gereklidir. Bu derlemede radyofarmasötiklere uygulanan kalite kontrol testleri, hastane radyofarmasi laboratuvar tipleri ve İyi Radyofarmasi Uygulamaları (GRP) ele alınacaktır.*

Sonuç ve Tartışma: *Radyofarmasötikler, farmakopelerin ilgili bölümlerinde belirtilen standartlara uygun olarak hazırlanmalıdır. Her radyofarmasötik serisi için farmakopelerde belirtilen testler ve kayıtlar tutulmalıdır. Radyofarmasötiklerin üretimi ve hazırlanması, steril preparatlar için İyi Üretim Uygulamaları ve radyoaktif ürünler için GRP uyarınca yapılmalıdır. Ancak kalite kontrol testlerini geçen radyofarmasötikler, doz kalibratörlerinde doz ölçümleri yapıldıktan sonra hastalara verilebilir. Böylece hastanın güvenliği ve faydası maksimize edilirken risk minimuma indirilir. Yarı ömrü kısa olan bazı radyofarmasötikler kalite kontrol testleri tamamlanmadan kullanılmaktadır. Bu durumda kalite güvence sisteminin etkinliği ve devamlılığı uygun aralıklarla test edilmelidir. Hastane radyofarmasi laboratuvarları tarafından yapılan işlemlere göre uluslararası standartlar Seviye IA/B, Seviye IIA/B ve Seviye IIIA/B/C olarak belirlenmişitr. Radyofarmasötiklerin kalite güvencesi, GRP kapsamında yeterli sayıda eğitimli personel, kalibre ve kontrolleri yapılmış cihazlar, uygun maddeler ve her aşamada belirlenen testlerin yapıldığı ve sonuçların doğru ve düzenli olarak kayıt altına alındığı bir çalışma düzeni ile sağlanır.*

Anahtar kelimeler: *İyi radyofarmasi uygulamaları, radyofarmasötikler, radyofarmasi laboratuvarı, kalite güvencesi, kalite kontrol*

INTRODUCTION

Radiopharmaceuticals are sterile and pyrogen-free drug formulations, which are mostly prepared to be administered intravenously to patients for diagnosis and treatment in nuclear medicine [1,2]. The most important difference from traditional drug formulations is that they contain a short half-life radionuclide in their structure. Unlike traditional drugs, they are produced, quality control tests are performed and administered to patients within the same working day [3]. Because some radionuclides have short half-life like ^{11}C, ^{13}N, ^{15}O, ^{18}F, these radiopharmaceuticals do not allow all quality control tests to be completed before being administered to patients. The quality control tests of these radiopharmaceuticals are specified in the relevant pharmacopoeias, which should be done before administration to the patient or which ones can be done retrospectively [4,5].

The purpose of quality control tests is to ensure that radiopharmaceuticals are administered to humans effectively and safely. Quality control of radiopharmaceuticals protects patients from unnecessary radiation exposure and side effects. It provides image quality and accurate diagnostic information in diagnosis, and maximizes patient benefit by providing maximum effect in treatment [6].

Quality assurance is a system that includes all the necessary components to ensure the safety, efficacy and purity of radiopharmaceuticals [7]. This system consists of many components. These are:

1. A sufficient number of personnel who have received the necessary training
2. A properly planned and traceable laboratory
3. Adequate equipment with proper calibration and maintenance
4. Documentation consisting of appropriate job descriptions and traceable regular records
5. Suitable chemicals and auxiliaries
6. Appropriate quality control tests at every stage [7]

Before the radiopharmaceuticals are administered to the patient, differential tests are performed quickly and effectively. These tests can be examined under four groups as physicochemical tests (radioactivity, radionuclidic purity, radiochemical purity and chemical purity), biological tests (sterility, pyrogenicity), pharmaceutical tests (appearance, color, pH, mean particle size, particle distribution, ionic strength, isotonicity, and osmolality) and toxicity tests [8]. In this review, quality control tests of radiopharmaceuticals, hospital radiopharmacy laboratory types and Good Radiopharmacy Practices (GRP) to ensure quality assurance of radiopharmaceuticals will be discussed.

Physicochemical Tests of Radiopharmaceuticals

Radioactivity

Radioactivity is the number of nuclear transformation per unit time in the amount of radioactive preparation. The unit of radioactivity Becquerel (Bq) expresses the number of transformations per second [9]. When working with radiopharmaceuticals, since it is a very small unit in practice, multiples such as kBq (10^3 Bq), MBq (10^6 Bq) and GBq (10^9 Bq) are used instead of Bq. To measure radioactivity, dose calibrators measure in micro Curie (μCi), mCi or MBq, GBq. There are well-type gas ionization chamber or dose calibrator systems to measure the radioactivity delivered to the patient. These devices must pass certain tests to achieve the correct activity. The dose calibrator quality control tests should be carried out at the installation stage and at the specified periodic intervals after installation. These tests are accuracy, stability, linearity, and geometry [10-12]. The acceptable limits of the dose that should be given to the patient according to the rules of the Nuclear Regulatory Commission (NRC) is ±10%. If the deviation in the dose calibrator is greater than 10%, the device must be repaired, recalibrated or replaced [13-15].

Radionuclidic identity

In order to determine the identity of the radionuclide in pharmacopoeias, some tests depending on the half-life and energy of the radionuclide are recommended [4,5]. The energy test is done by taking the gamma spectrum of the radionuclide, which is the unique identifier for identity testing [16]. It is

difficult to perform in the radiopharmacy laboratory as it requires equipment. The spectrometer system must also be calibrated for accurate measurement. In the ionization chamber linearity test proposed to determine the identity of the radionuclide, the radioactivity is measured at regular intervals for about 3 half-lives and plotted against time. The slope gives the decay constant λ. Half-life is calculated from the activity at time t with the formula $In(A_t)=In(A_0) - \lambda$ (Eq.1).

$T_{1/2} = In(2)/\lambda$ (Eq. 2)

A_t = The activity at time t

A_0 = The activity at the beginning

$T_{1/2}$ = Half-life of radionuclide

λ = Decay constant of radionuclide

Radionuclidic purity

Radionuclidic purity is defined as the ratio of the activity of the radionuclide to the total radioactivity. The undesired radionuclides can belong to the same element as the desired radionuclide or to a different element. The purpose of radionuclide purity control is to protect the patient from unnecessary radiation and to use the radiopharmaceutical effectively [17]. The radionuclide must be free from all other species. Impurities arise from the production method of the radionuclide: Ge-68 in Ga-68 eluate in $^{68}Ge/^{68}Ga$ generator, Sr-82 in Rb-82 eluate in $^{82}Sr/^{82}Rb$ generator, or Mo-99 in Tc-99m eluate in $^{99}Mo/^{99m}Tc$ generator.

Radionuclidic purity is determined by measuring the type of radiation emitted from each radionuclide and its half-life. Gamma-emitting radionuclidic impurities are measured by multi-channel analyzer systems with NaI(Tl) or Ge(Li) detectors, while pure beta-emitting radionuclides are measured with beta spectrophotometer or liquid scintillation methods [18]. Identifying pure beta emitters is not as easy as gamma emitters due to the counting problem. Mo-99 impurity in Tc-99m is practically measured by gamma photon absorption (lead shield) method. $^{99}Mo/^{99m}Tc$ generator is loaded on glass column (Al_2O_3), Mo-99 activity is adsorbed on column material in the form of MoO_4^{-2} (molybdate). The ^{99}Mo activity in the eluate should be less than 0.15 $\mu Ci.mCi^{-1}$ Tc-99m. The quantities of impurities should not exceed acceptable limits. The molybdenum impurity in the product obtained from the $^{99}Mo/^{99m}Tc$ generator at each eluating and the expiry time of Tc-99m should be determined. Expiry time should not exceed 12 h after eluating. NRC has set acceptable limits for each radionuclide [19].

Radiochemical purity

Radiochemical purity indicates the ratio of radionuclide contained in the radiopharmaceutical in the chemical compound and is expressed in percent. Radiochemical purity is calculated by the ratio of the activity in the desired chemical form to the total radioactivity. Radiochemical impurities are caused

by changes in solution temperature or pH, light, the presence of reduced or oxidized agents, and structural deterioration due to radiolysis. The distribution in the biological system and the absorbed radiation dose are directly related to the radiochemical purity. This situation causes low quality images to be taken and the patient to receive high doses of radioactivity due to the weak localization of the radiopharmaceutical in the desired area and the high ground activity from the surrounding tissues. The reason for the radiolabeled compounds to decay by radiolysis is the type and energy of radiation the radionuclide has. As a result of the absorption of the radioactivity of the radiolabeled molecule, free radicals with unshared electrons are formed and these free radicals cause other molecules to degrade. Secondly, chemical structures such as hydrogen peroxide (H_2O_2) or hydrogen dioxide (HO_2) formed as a result of the radiolysis of water (H_2O) cause the labeled molecule and other molecules to deteriorate. Particular radiation releases its energy at a shorter distance than gamma radiation. In order to ensure the stability of radiopharmaceuticals, substances such as ascorbic acid, *p*-aminobenzoic acid and gentisic acid are added to the formulations as antioxidant agents in some cases [20,21].

There are chromatography methods such as gel chromatography, gas chromatography (GC), high performance liquid chromatography (HPLC), and paper chromatography (PC) to determine radiochemical purity. In the hospital radiopharmacy laboratory, the applicable quality control method is PC or thin layer chromatography (TLC) in terms of being fast and economical [20].

Chromatography is a method of separating and purifying the components that make up the chemical mixture in a two-phase system, one of which is stationary and the other is mobile phase. It is based on the principle that the components are drifted with different speeds on the stationary phase with the help of the moving phase [22]. Radiochromatography, unlike ordinary chromatography, detects radioactive species based on their location rather than their chemical or physical properties [23]. Paper is used as the stationary phase in PC. Separation is ensured by passing a solvent that will provide separation from the paper, by making use of the different speed of the substances to be separated on the paper. The difference of TLC from PC is that instead of paper, silica gel, aluminum oxide, aluminum silicate or cellulose coated papers (Whatman 3M) are used and the separation process is completed faster and in a short time. The Relative front (R_f) value of a compound is descriptive as the distance that compound travels through a liquid through a stationary phase. The R_f value must be between 0-1. If the administered compound remained at the application point, R_f is indicated as 0, if it progressed to the extreme point, it is designated as R_f 1 [23,24]. Figure 1 shows the calculation of the R_f value on the strip. While Table 1 shows R_f values of radiopharmaceuticals labeled with Tc-99m, Table 2 shows R_f values of various radiopharmaceuticals labeled with radionuclides other than Tc-99m [25,26].

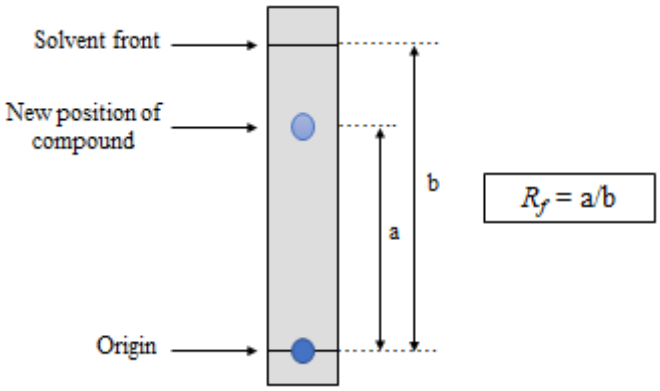

Figure 1. Determination of R_f value

Table 1. Chromatographic data of radiopharmaceuticals labeled with Tc-99m

Radiopharmaceutical	**Chromatographic System**	***R_f*** **Radiopharmaceutical**
^{99m}Tc-Sodium pertechnetate	Chromatography paper / Acetone: 2N Hydrochloric acid (80:20)	0.9
^{99m}Tc-Sodium pertechnetate	ITLC-Silica gel / 0.9% NaCl	1.0
^{99m}Tc-Sodium pertechnetate	Chromatography paper / Water: Methanol (20:80)	0.6
^{99m}Tc-(pyro and trimeta) phosphate	Chromatography paper / Physiological saline	0.0-0.1
^{99m}Tc-(pyro and trimeta) phosphate	Chromatography paper / Methyl Ethyl Ketone	0.0-0.1
^{99m}Tc-Albumin aggregate	Chromatography paper / Dilute methanol (7:10)	0.0-0.1
^{99m}Tc-Albumin aggregate	ITLC-Silica gel / 2-Butanone	0.0-0.1
^{99m}Tc-Arkitumomab	Silica gel / Acetone	0.0-0.1
^{99m}Tc-Bisisate	Silica gel / Ethyl acetate	0.4
^{99m}Tc-Bisisate	ITLC-Silica gel / Saturated NaCl	0.0-0.1
^{99m}Tc-Bisisate	ITLC-Silica gel / Methanol: Ammonacetate (50:50)	0.9-1.0
^{99m}Tc-Etifenin	Chromatography paper / Water: Acetonitrile (40:60)	0.9-1.0
^{99m}Tc-Etifenin	Chromatography paper / Methyl Ethyl Ketone	0.0-0.1
^{99m}Tc-Gluconate	Silica gel / 0.9% NaCl	0.9-1.0
^{99m}Tc-Gluconate	Silica gel / Methyl Ethyl Ketone	0.0-0.1
^{99m}Tc-Gluseptat	Chromatography paper / Acetone	0.0-0.1
^{99m}Tc-Human albumin	Silica gel / Methyl Ethyl Ketone	0.0-0.1

Table 1 (*continued*). Chromatographic data of radiopharmaceuticals labeled with Tc-99m

Radiopharmaceutical	Chromatographic System	R_f Radiopharmaceutical
^{99m}Tc-Stannous pyrophosphate	Silica gel / Sodium acetate	0.9-1.0
^{99m}Tc-Stannous pyrophosphate	Silica gel / Methyl Ethyl Ketone	0.0-0.1
^{99m}Tc-Colloidal tin	Silica gel / 0.9% NaCl	0.0-0.1
^{99m}Tc-Colloidal Rhenium sulfide	Chromatography paper / Physiological saline	0.1
^{99m}Tc-Colloidal sulfur	Chromatography paper / Physiological saline	0.1
^{99m}Tc-Lidophene	Silicylic acid impregnated fiberglass paper tape / Nitrogen-leached solution of NaCl	0.0-0.1
^{99m}Tc-Medronat	Silica gel / Sodium acetate	0.0-0.1
^{99m}Tc-Nofetumomabmer pentane	Silica gel / 0.73 N Trichloroacetic acid	0.0-0.1
^{99m}Tc-Oxydronate	Chromatography paper / Physiological saline	0.9-1.0
^{99m}Tc-Oxydronate	Silica gel plate / Methyl Ethyl Ketone	0.0-0.1
^{99m}Tc-Pentetate	Silica gel / 0.9% NaCl	0.9-1.0
^{99m}Tc-Pentetate	Silica gel plate / Methyl ethyl ketone	0.0-0.1
^{99m}Tc-Sestamibi	Octadecylsilyl silica gel plate / Tetrahydrofuran: Ammonium acetate: Methanol: Acetonitrile (10:20:30:40)	0.3-0.6
^{99m}Tc-Sestamibi	Aluminum oxide coated TLC / Ethanol	0.9-1.0
^{99m}Tc-Sucimer	Silica gel plate / Methyl Ethyl Ketone	0.0-0.1
^{99m}Tc-Sulfur colloid	Chromatography paper / Methanol	0.0-0.1
^{99m}Tc-Tetrofosmine	ITLC-Silica gel / Acetone: Dichloromethane (35:65)	0.5
^{99m}Tc-Dimercaptosuccinic acid	ITLC-Silica gel / 2-Butanone	0.0-0.1
^{99m}Tc-Diphosphonates	ITLC-Silica gel / 1M NaAcetate	0.9-1.0
^{99m}Tc-Diphosphonates	ITLC-Silica gel / 2-Butanone	0.0-0.1
^{99m}Tc-Diethylene Triamine Penta Acetate	ITLC-Silica gel / NaCl	0.9-1.0

Table 1 (*continued*). Chromatographic data of radiopharmaceuticals labeled with Tc-99m

Radiopharmaceutical	Chromatographic System	R_f Radiopharmaceutical
^{99m}Tc-Diethylene Triamine Penta Acetate	ITLC-Silica gel / 2-Butanone	0.0-0.1
^{99m}Tc-Ethyl Cysteinate Dimer	Baker Silica gel / Ethylacetate	0.9-1.0
^{99m}Tc-Hexamethylene-propyleneamine oxime	ITLC-Silica gel /2-Butanone	0.9-1.0
^{99m}Tc-Hexamethylene-propyleneamine oxime	ITLC-Silica gel / 0.9% NaCl	0.0-0.1
^{99m}Tc-Dimethyl-acetanilide-iminodiacetic acid	ITLC-Silica gel / 0.9% NaCl	0.0-0.1
^{99m}Tc-Dimethyl-acetanilide-iminodiacetic acid	ITLC-Silica gel / 50% Acetonitrile	0.9-1.0
^{99m}Tc-Ethylenedicysteine	ITLC-Silica gel / 2-Butanone	0.0-0.1
^{99m}Tc-Ethylenedicysteine	ITLC-Silica gel / 0.3M Acetic acid	0.9-1.0
^{99m}Tc-Monoclonal Antibodies	ITLC-Silica gel / 0.9% NaCl	0.0-0.1

Table 2. Chromatographic data of various radiopharmaceuticals labeled with radionuclides other than Tc-99m

Radiopharmaceutical	Chromatographic System	R_f Radiopharmaceutical
^{18}F-Alovudin	Silica gel / Water: Acetonitrile (5:95)	0.7
^{18}F-Fluorodeoxyglucose	Silica gel / Water: Acetonitrile (5:95)	0.0
^{18}F-Fluorodopa	Octadesylsilyl silica gel / Methanol: Water (50:50)	0.3
^{18}F-Fluoroethyl-L-Tyrosine	Silica gel / Acetic acid: Methanol (10:90)	0.7
^{18}F-Fluorocholine	Silica gel / Acetonitrile: NaCl solution (50:50)	0.5
^{18}F-Fluoromisonidazole	Silica gel / Water: Acetonitrile (5:95)	0.8
^{68}Ga-Edotreotide	Silica gel / 77 $g.L^{-1}$ Ammonium Acetate solution in water: Methanol (50:50)	0.8-1.0
^{68}Ga-Chloride	Silica gel / 77 $g.L^{-1}$ Ammonium Acetate solution in water: Methanol (50:50)	0.0-0.2

Table 2 (*continued*). Chromatographic data of various radiopharmaceuticals labeled with radionuclides other than Tc-99m

Radiopharmaceutical	Chromatographic System	R_f Radiopharmaceutical
^{111}In-Ibritumomab	Silica gel / 0.9% NaCl	0.0-0.1
^{111}In-Kapromab Pentetate	Silica gel / 0.9% NaCl	0.0-0.1
^{111}In-Chloride	Silica gel / NaCl solution (pH:2.3)	0.5-0.8
^{111}In-Pentetate	Silica gel / 0.9% NaCl	0.9-1.0
^{111}In-Satumomab Pentetate	ITLC-Silica gel / 0.9% NaCl	0.0-0.1
^{111}In-Octreotide	ITLC-Silica gel / 0.1M Na-Citrat pH:5	0.0-0.1
^{90}Y-Ibritumomab Tiuxetan	Silica gel / 0.9% NaCl	0.0-0.1
^{125}I-Albumin	Chromatography paper / Diluted methanol (7:10)	0.0-0.1
^{125}I-Iotalamate sodium	Chromatography paper / Methanol (adjusted to pH 3-6 with 2N Sulfuric acid): Ammonium hydroxide (100:1.5)	0.0-0.1
^{131}I-Rosebengal sodium	Chromatography paper / N Acetic acid	0.0-0.1
^{51}Cr-Edetat	Chromatography paper / Concentrated Ammonia: Ethanol: Water (1:2:5)	0.8-0.9
^{51}Cr-Sodium chromate	Chromatography paper / Ammonia: Ethanol: Water (25:50:125)	0.9
^{32}P-Chromic phosphate	Chromatography paper / Water	0.0-0.1
^{11}C-Methyl-L-Methionine	Octadecylsilyl silica gel / Methanol: Water (50:50)	0.58
$^{177}Lu^{3+}$	Silica gel / NaCl solution (pH:2.3)	0.4-0.7

Each radiopharmaceutical must be tested for radiochemical purity before being administered to the patient. In terms of radiochemical purity, only free Tc-99m is expected in eluating product obtained from generator.

The presence of Reduced/Hydrolyzed (R/H) Tc-99m in the eluating solution creates an impurity. In radiopharmaceutical kits, a Tc-99m substrate becomes captive in a special organ system by binding to the molecule. It may cause some problems in imaging by creating both free Tc-99m ($^{99m}TcO_4^-$) and R/H Tc-99m (TcO_2) radiochemical impurity that occurs during the radiopharmaceutical preparation process [20].

Radiochemical impurities may cause difficulty in evaluating images and even inaccurate clinical diagnosis. Therefore, it is important to effectively couple the radionuclide and the desired molecule to ensure the accuracy of reported disease diagnoses. The desired efficacy and safety will not be achieved

after treatment with radiopharmaceutical with low binding activity. United States Pharmacopeia (USP) has established minimum standard binding efficiencies for many radiopharmaceuticals [4,5]. The rate of radiochemical impurities can be at most 5% [27].

Chemical purity

Chemical impurities are all non-radioactive chemical structures in the radiopharmaceutical preparation and cause adverse effects directly or by radiolabeling. The most common chemical impurities are Al^{+3} for ^{99m}Tc radiopharmaceuticals and Kryptofix 2.2.2 for ^{18}F-FDG. According to USP standards, the amount of Al^{+3} ions in the Tc-99m eluate should not exceed 10 $\mu g.mL^{-1}$ [4,5]. If there is more, colloidal Tc-Al particles are formed. These particles can be accumulated in the liver and cause cell damage by aggregation, with capillary blockage when larger particles appear, and by binding to red blood cells. The amount of chemical impurities is measured by the spectrophotometric method. A simpler method to detect aluminum is that the indicator paper gives the reagent red in the presence of Al^{+3}. A standard solution of 10 $\mu g.mL^{-1}$ of aluminum is used for color analysis. All commercial kits contain stannous ions as reducing agents. If there is too much stannous ions in the kit, it may cause some problems; for example, while the bone should be visible, the liver is visible. Another problem is that the excess stannous remaining in the circulation is destroying the red blood cells and collecting in the spleen [27].

Biological Tests of Radiopharmaceuticals

Each parenterally injected product must be sterile, pyrogen-free, and non-toxic. Biological tests are performed during and after production to ensure that radiopharmaceuticals are sterile and clear of pyrogens. In order for the product to be sterile and free of pyrogens, it must be manufactured under sterile conditions, with sterile environments and materials. Toxic dose should be determined in animal studies before being used in humans.

Sterility

Sterile solution is the solution medium in which there are no pathogenic or non-pathogenic living organisms. Sterilization can be done by autoclaving at 121°C at 15 psi pressure or by 0.22 μm membrane filtration sterilization under aseptic conditions. Sterility control is performed to show that there is no live bacteria or microorganism in the radiopharmaceutical preparation. It is carried out by taking a sample from the drug and making a culture in a suitable medium. Incubate for 14 days at 30-35°C in liquid thioglycolate medium or incubate for 14 days at 20-25°C in soy-casein medium. If there is no microbial growth, the drug is sterile [28].

Many radiopharmaceuticals are produced and used on the same day. Since the sterility test is time-consuming, the radiopharmaceutical which has radionuclide with short half life, is sent to the user before the sterility test is completed, and the sterility results are recorded retrospectively. Clean environmental

conditions should be maintained during production, High Efficiency Particulate Air (HEPA) filters take particles of 0.3 μm and larger, sterile disposable materials, sterile chemicals (water for injection, NaCl, etc.) should be used. If aseptic conditions are applied correctly, the possibility of bacterial contamination is reduced. It is recommended to take samples from the radiopharmaceutical prepared periodically once a week and send it to the microbiology laboratory for bacteriological testing [3].

Pyrogenicity

Pyrogens are metabolic wastes of living organisms, or non-living organisms. Pyrogens are typical bacterial endotoxins. They cannot be destroyed in the autoclave and cannot be separated by membrane filtration. Although the solution is sterile, it may contain pyrogen. The way to prevent it is to use high quality water and chemicals. The patient experiences fever, chills, headache and chest pain 45-90 min after the injection of the pyrethetic substance, and this non-lethal situation ends after 3-4 h. Pyrogen test is determined by two different methods.

Limulus Amebocyte Lysate (LAL) test

Gram negative endotoxin is the most important source of pyrogen contamination. The LAL test is a fast and sensitive method that detects the presence of pyrogen and displays pyrogens at the $ng.mL^{-1}$ level. The protein isolated from the blood cells of the horseshoe crab (limulus polyphemus) forms a matte gel with nanograms or greater concentrations of gram negative bacterial endotoxin. The sample to be tested is incubated with lysate at 37°C for 60 min. Formation of a matt gel indicates the presence of pyrogen [29].

Rabbit pyrogenicity test

In the rabbit test, the test sample is injected into 3 rabbits. After injection, rectal temperature is recorded once an hour for three hours. It is compared with the temperature before injection. A rise in temperature of 0.6°C in each rabbit or a total temperature of 1.4°C in three rabbits is indicative of the presence of pyrogenic matter. The rabbit test method, which is decided by considering the rise in fever of rabbits, is no longer used [30].

Radioassay/radioactive dose for the patient

During the preparation of the radiopharmaceutical and before it is given to the patient, the radioactivity of the radiopharmaceutical should be known according to the dose calculation made for each patient. The amount of radioactivity in the radiopharmaceutical that is drawn into the injector to be administered to the patient is measured with a dose calibrator. The amount of radioactivity is given in Ci or Bq. The activity of the radiopharmaceutical decreases over time depending on the half-life of the radionuclide used [31]. The following formula is used to calculate the activity of the pharmaceutical over time (Eq. 3):

$A_t = A_0 \times e^{-0.693 \times t / T_f}$ (Eq. 3)

A_t = Activity (Bq or Ci) at time t

A_0 = Activity (Bq or Ci) in original sample

t = Time

T_f = Physical half-life of radionuclide

Pharmaceutical Tests of Radiopharmaceuticals

Radiopharmaceuticals must have the proper ionic structure, isotonicity, and osmolality in order to be used in humans. After each preparation, the radiopharmaceutical should be examined visually. The mean particle size and size distribution should be determined, as well as the quantity of particles to be supplied to the patient. The pH of the first product must be controlled in each batch prepared. An injectable drug's isotonicity should be the same as a 0.9% sodium chloride solution.

Appearance and color

The physical appearance of a radiopharmaceutical after preparation and during use is specified in the relevant monograph of the relevant pharmacopeia [4,5]. The radiopharmacist should check the clarity and color of the radiopharmaceuticals after each preparation. If the radiopharmaceutical is not in particle form, but in solution form, it should not contain particles.

pH

In the dilution of radiopharmaceuticals, liquids with an ionic structure and pH long-term value that will not disturb the stability and physiological compatibility are used. For the stability of the radiopharmaceutical, all radiopharmaceuticals are formulated in the optimum pH range. The most suitable pH value for parenteral use is the blood pH value of 7.4. At the same time, due to the buffering property of blood, radiopharmaceuticals can be prepared between pH 2-9. In clinical routine use, pH value measurement with pH paper is a simple and fast method [2,6].

Mean particle size and size distribution

Mean particle size and size distribution is an important test that must be controlled in order to achieve the desired distribution of the radiopharmaceutical in the biological system. The particle-containing radiopharmaceutical is heterogeneous, and the mean particle size is determined by light microscope, hemocytometer or dynamic light scattering. It contains two main types of radiopharmaceutical particulate structures: albumin microspheres [macro aggregated albumin (MAA), human albumin microspheres (HAM), human serum albumin (HSA)] for lung scintigraphy and colloids for the reticuloendothelial system. According to USP standards, at least 90% of the particles to be used for lung imaging should be 10-90 μm in diameter [4,5]. Smaller particles easily pass through the lungs

and are accumulated in the reticuloendothelial system (liver, bone marrow). No particle should exceed 150 μm. The number of particles is determined according to the condition of the disease and the child patient. Particles should be in the range of 0.1-1 μm for liver and spleen imaging and 0.01-0.3 μm for lymphoscintigraphy. Dynamic light scattering is the best methods for measuring mean particle size and size distribution [32,33].

Ionic strength, isotonicity, and osmolality

The final form of the radiopharmaceutical must be isotonic, in other words the ionic strength must be the same as the blood. Isotonic fluid has the same osmotic pressure as human serum. Radiopharmaceuticals with 250-350 $mOsm.kg^{-1}$ are considered isotonic. Isotonia test is done using an osmometer. Osmolarity controls the transitions between intracellular and extracellular. When an equal concentration of solute occurs between the inside and outside of the cell, the cells are not damaged because the pressure inside and outside the cell will be equal. Hypertonic or hypotonic fluid damages cells. 0.9% sodium chloride solution is an isotonic solution, and the applied radiopharmaceuticals are usually injected in this solution [34]. Due to the blood's high dilution and buffering capacity, the tolerances for pH and osmolality of intravenous injections are broad. However, the osmolality tolerances are critical for intrathecal administrations. The preparation and selection of radiopharmaceuticals, and diluents used for intrathecal administration requires special consideration.

Toxicity Tests of Radiopharmaceuticals

Acute and chronic toxicity test of radiopharmaceuticals is carried out by animal testing. After the autopsy performed 2-6 weeks after the radiopharmaceutical administration, toxicity limits are determined by cell culture study. The dose that kills 50% of the animals is shown as LD_{50} [3].

Hospital Radiopharmacy Laboratory Types and Required Quality Controls

The procedures performed in hospital radiopharmacy laboratories around the world are classified under 3 main categories [35-37].

Operational level I

Operational level I A

It includes radiopharmaceuticals, in the final form, purchased from authorized manufacturers, in single or multiple dose form where no combination is required. Quality control studies consist of measuring the radioactive dose of the radiopharmaceutical. The consistency of the dose calibrator should be evaluated daily with a long half-life radionuclide such as Cs-137 [35-37].

Operational level I B

This level of operation includes the preparation of ready-to-use injections of Sr-90 and Sm-153 used for therapy and pain relief therapy, and other ready-to-use open source radionuclides. Periodically, radionuclidic and radiochemical impurities should be checked [35-37].

Operational level II

Operational level II A

Routine use of the Tc-99m generator involves the reconstitution of pre-sterilized radiopharmaceutical cold kits. Quality controls are quality controls on generator and generator eluating in addition to Operational Level I. In the first eluating, radionuclidic impurity test, sterility, radiochemical impurity and aluminum ion contamination should be checked. Radiochemical impurity tests should also be performed before the radiopharmaceuticals are administered to the patient [35-37].

Operational level II B

It involves radiolabeling of blood cells taken from the patient to display infection or inflammation. In quality controls, the shelf life of ^{99m}Tc-HMPAO, ^{111}In-Oxine and Tc-99m colloids should be considered and the radiolabeling percentage of leukocytes should be calculated routinely [35-37].

Operational level III

Operational level III A

This level covers radiopharmaceuticals prepared for diagnostic applications. Procedures in Level I and II, sterility test, bacterial endotoxin test, microbiological and pyrogenicity tests, specific activity, chemical purity, HPLC, GC, TLC, radiochemical purity, stability and toxicity studies are required for quality control studies [35-37].

Operational level III B

This level involves the preparation of radiopharmaceuticals (Metaiodobenzylguanidine (MIBG) radioionidation, ^{188}Re-lipiodol, etc.) for therapeutic applications for research and development purposes. Radionuclidic purity of the radiopharmaceutical is important in quality control [35-37].

Operational level III C

This level includes the synthesis of Positron Emission Tomography (PET) radiopharmaceuticals, research and development purpose radiopharmaceuticals produced from long-life generators such as Ga-68 and Re-188 generators. Quality control of radiochemical purities must be done quickly by HPLC. Sterility, pyrogenicity and physicochemical tests should also be performed routinely [35-37].

Good Radiopharmacy Practices (GRP)

Regarding the preparation and administration of radiopharmaceuticals, GRP combines the principles of traditional Good Manufacturing Practices (GMP) of pharmaceuticals with radioprotection concepts. The components of GRP are personnel and resources, qualifications, quality assurance, facility and equipment, quality control, documentation and labeling [38,39].

Personnel and resources

In radiopharmacy lab, radiopharmacist is the responsible person which the owner of this area. Also, the number of personnel should be such that all necessary procedures are completed before the application of the prepared radiopharmaceutical. It is recommended that the duties and responsibilities of all personnel are clearly defined in written documents. In GRP, an organizational chart is created between the preparation steps and personnel responsibilities. All operations must be carried out under the control of the responsible person (radiopharmacist). All personnel in charge from the preparation to distribution of radiopharmaceuticals should be properly trained in quality systems, GRP and all regulatory requirements related to radiopharmaceuticals. Personnel exposure to radiation should be monitored by approved personnel dosimeters that are regularly checked and readings are recorded. After the radiopharmaceutical preparation is completed, it should be checked whether there is radioactive contamination in both the staff and the working area with appropriate monitors [39,40].

Qualifications:

- The radiopharmacist must establish procedures for the inspection and evaluation of incoming materials and ensure that every incoming material is examined and evaluated before it is used against specifications.
- The person responsible for quality assurance of radiopharmaceuticals should establish and manage the overall quality assurance system and verify that the documentation is written correctly.
- The person responsible for the production of radiopharmaceuticals must approve the production processes, evaluate, sign and store production records.

The person responsible for quality control must describe the specifications, test methods and other quality control procedures. It must evaluate, sign and keep quality control reports and records [39,40].

Quality assurance

It is recommended to establish a quality assurance program to comprehensively design and correctly implement a quality assurance system, taking into account the appropriate risk assessment in GRP. Risk assessment plays an important role in all stages involved in the preparation of radiopharmaceuticals. The quality assurance team should inform the persons involved in the preparation

of radiopharmaceuticals according to up-to-date information, and declare the necessary measures in writing to ensure that the radiopharmaceuticals are released, stored and transported in a manner that ensures the desired quality throughout the shelf life and in accordance with the expiry date [7].

Facility and equipment

Facilities should be designed to ensure proper handling of materials and equipment, and prevent contamination of the equipment or product according to personnel or environmental conditions. It should be such that all equipment used in production (eg particle accelerator, synthesis units or other special equipment) is located and maintained in an easily accessible manner to all work areas in the normal production stage. Access to workplaces should be limited to responsible personnel. In the preparation of radiopharmaceuticals, the same area or room can be used for multiple purposes. However, in the case of multiple radiopharmaceutical preparations, it is important to develop the appropriate level of control required to avoid confusion and contamination. In order to avoid confusion and contamination, different production areas should be clearly defined and segregated, especially with regard to unidirectional material flow, intermediate and finished products. The preparation of radiopharmaceuticals, quality control and storage of all approved ingredients, including laboratory procedures (such as release testing), containers and lids can be done in the same room. All equipment can potentially affect the quality and purity of radiopharmaceuticals or give incorrect or invalid test results when used or not performed incorrectly. It is therefore essential to demonstrate that the equipment is fit for the intended purposes, is properly installed, maintained and can produce valid results over and over again [41].

Quality control

It is recommended that any quality control method required for radiopharmaceuticals have the appropriate equipment to perform its function. For this purpose, the dose calibrator, radioactive TLC scanner, HPLC device should be checked and maintained at recommended times [8].

Documentation

Quality control and assurance is based on an appropriate documentation system, organized in written or electronic form, containing any documents, standart operating procedures (SOPs) and records regarding any relevant step in the radiopharmaceutical preparation process to ensure traceability of the entire process. Written procedures should cover how to select each material (ingredients, containers and lids), the preparation process and all controls. The processes must cover the life of a material from receipt of the material to final consumption. Records should be kept accessible and readily available to any internal or external auditor within a reasonable time during the audit. Records must be kept for at least 1 year. However, archiving time must comply with local and national regulations [42].

Labeling

Labels can be computer-generated or handwritten. It is common practice to prepare most of the labeling ahead of time due to radiation exposure concerns. For example, an empty product bottle can be pre-labeled with partial information (product name, serial number, date) prior to infiltration of the radioactive product, and upon completion of the quality control test, the outer shielded box is labeled to contain the required information (radioactivity). A final check should be performed to verify that the correct and complete label is attached to the can and container [43].

RESULT AND DISCUSSION

Quality control tests for radiopharmaceuticals are specified in pharmacopoeias. Quality control procedures should be carried out at all operational levels and accurate and regular retrospective records should be kept. Quality assurance and quality products are obtained with calibrated and controlled devices, quality suitable materials, working order in which determined tests are performed by trained personnel at every stage and a properly planned laboratory according to GRP rules.

AUTHOR CONTRIBUTIONS

Conception: *M.E., R.S.O., D.İ.Ö.*; Design: *M.E., R.S.O., D.İ.Ö.*; Supervision: *R.S.O., D.İ.Ö.*; Resources: *M.E., R.S.O., D.İ.Ö.*; Materials: *M.E., R.S.O., D.İ.Ö.*; Data collection and/or processing: *M.E.*; Analysis and/or interpretation: *M.E.;* Literature search: *M.E.*; Writing manuscript: *M.E.*; Critical review: *M.E., R.S.O., D.İ.Ö.*; Other: -

CONFLICT OF INTEREST

The authors state that there are no actual, potential, or perceived conflicts of interest for this paper.

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