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Production of clinical radiopharmaceuticals: general pharmaceutical and radioanalytical aspects

Alexander Schmidt[1] · Margret Schottelius[1] · Michael Herz[2] · Hans-Jürgen Wester[1]

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Abstract Due to successes in the development on new and powerful radiopharmaceuticals, in particular of tracers for positron emission tomography, the production of a continuously expanding spectrum of radiopharmaceuticals has become more important, even for small nuclear medicine facilities. This short review summarizes and briefly describes typically established radioanalytical routines in the quality control of radiopharmaceuticals as well as the corresponding fundamental legal documents and guidelines.

Keywords Radiopharmaceuticals · GMP production · Quality control · Good manufacturing practice · Radiopharmacy

Introduction

The application of diagnostic radiopharmaceuticals in modern nuclear medicine can be defined as the use of radioactive probes with the aim to localize a disease and to characterize its extent and its kinetics. Ideally, this is achieved by using a targeted probe that binds with high affinity and selectivity to an extracellular or intracellular molecular target, e.g., an enzyme, a receptor, an antigen etc., whose (over)expression correlates with the extent of the disease. For positron emission tomography (PET), short lived positron emitters are nowadays routinely produced in more and more powerful compact cyclotrons by proton irradiation of small liquid or gas targets with protons [1, 2]. Apart from the frequently used cyclotron-produced PET-radionuclides ^{18}F, ^{11}C, ^{15}O and ^{13}N, that are mostly converted to the desired radiopharmaceuticals in two-to-multistep automated procedures, positron-emitting radiometals have become increasingly important [3–6]. These radionuclides, i.e., ^{68}Ga, ^{64}Cu and ^{89}Zr, can be rapidly complexed by chelator-conjugated vectors (small peptides or proteins) within a few minutes in aqueous buffer in nearly quantitative yields. Furthermore, the same chelator-vector conjugates (such as DOTA peptides) are also often used for labeling with therapeutic M^{3+}-radionuclides such as ^{90}Y, ^{177}Lu or ^{213}Bi etc. During the last decade, this so called theranostic approach [7–9] that bridges the use of the same bioactive vector for a diagnostic application with the therapeutic option, has become very popular.

The prototype of a targeted 'bioactive' probe is 2-[^{18}F]fluoro-2-deoxy-glucose ([^{18}F]FDG), an analogue of glucose, that is transported via glucose transporters into the cell, subsequently phosphorylated by hexokinase (so called metabolic trapping) [10, 11]. [^{18}F]FDG is widely regarded as the "blockbuster" of PET [12], and more than 116.000 publications are listed under the keyword "FDG" in Thomson Reuters "Web of Science" [13]. [^{18}F]FDG also exemplifies the fact that targeting and detection of the rate limiting step (often the first step) of a biochemical process by a suitably designed radiotracer provides valuable information on the regulation of the entire pathway.

In order to avoid disturbance of the biochemical process of interest, radiopharmaceuticals are generally produced in high (or highest possible) specific activities. Obviously, 'contaminations' of a ready-to-use radiopharmaceutical

✉ Hans-Jürgen Wester
h.j.wester@tum.de

[1] Chair for Pharmaceutical Radiochemistry, Technischen Universität München, Walther-Meissner-Strasse 3, 85748 Garching, Germany

[2] Department of Nuclear Medicine, Klinikum r.d.Isar der Technischen Universität München, Ismaninger Strasse 22, 81675 Munchen, Germany

formulation with labeled or unlabeled species can compete with the binding of the radiopharmaceutical and thus can result in decreased signal intensity. Determination of the chemical purity and the consideration of the presence of unlabeled (but target-binding) species is of utmost importance for the calculation of the specific activity. In the case of [^{18}F]FDG, the presence of higher amounts of D-glucose and non-radioactive [^{19}F]FDG ($\leq$0.5 mg in the entire volume, e.g., FDG-TUM: $\leq$33.3 μg/ml; D-glucose: $\leq$500 μg/ml) does not alter the PET imaging results, as both rate limiting steps of the accumulation mechanism (transporter and enzyme) are only saturable in the presence of much higher amounts. In contrast, for receptor targeted probes, and in particular for small animal imaging applications in mouse models, where the human situation is reduced by a factor of 1/3000–1/4000 (body weight ratio), unsuitable specific activities or contaminations can significantly reduce the specific accumulation in the target tissue (in vivo competition effect) [14, 15]. Apart from the specific activity and the chemical purity, the radiochemical purity (presence of other labelled species) is one of the most relevant quality control parameters of radiopharmaceutical preparations. Radiochemical contaminations can result from incomplete final radio-HPLC purification (e.g., radiolabeled side products etc.), the use of impure radioisotopes (e.g., ^{177m}Lu from ^{177}Lu as therapeutic isotope) [16], impurities from radionuclide generators (e.g., breakthrough of the ^{68}Ge mother nuclide from ^{68}Ge/^{68}Ga-generators) [17], residual solvent contaminations (e.g., acetonitrile in ^{18}F-radiopharmaceutical production from incomplete evaporation steps), or the presence of free radioisotopes (e.g., free radiometal in radiochelate-based radiopharmaceuticals), to mention only a few. Finally, the unambiguous identification of the radionuclide incorporated into a radiopharmaceutical by means of γ-spectrometry, and, when necessary, the additional determination of the half-life (e.g., to discern one PET isotope from another), the confirmation of sterility, the absence of pyrogens, the pH, the visual aspect and the radioactive concentration are important quality control and release criteria in routine clinical radiopharmacies. Alongside with the suitable environment for radiopharmaceutical production under good manufacturing practice (GMP) conditions, this short review focuses on the state of the art radioanalytical methods and radiopharmaceutical aspects in modern clinical radiopharmacies. The review summarizes part of a presentation given at the first International Conference of Radioanalytical and Nuclear Chemistry in Budapest, May 2016.

Good manufacturing practice (GMP) and legislation

In addition to [^{18}F]FDG with almost full market availability and some other PET tracers with marketing authorization in only a few European countries, human application of radiopharmaceuticals in clinical practice (apart from clinical studies) is often based on exemptions from the need for a market authorization as stated in Directive 2001/83, Title II [18]. Here, the permission for 'extemporaneous' preparation of medicinal products such as the radiopharmaceuticals used is given when a medical prescription for an individual patient has been issued (magistral preparation or approach). Great variation, however, exists concerning the interpretation of this directive within Europe. The production of radiopharmaceuticals has to meet the European GMP requirements described in vol. 4 of the Eudralex (Guidelines for good manufacturing practices for medicinal products for human and veterinary use) [19] (Table 1). This web-based compendium summarizes the general rules in vol. 4, part 1–3 and gives specific information on dedicated topics in Annexes, i.e., in Annex 3 (manufacture of radiopharmaceuticals) and Annex 13 (manufacture of investigational medicinal products). Further requirements on the automated production and subsequent instrumental analysis prior to release are covered

Table 1 Selected documents related to good manufacturing practice (GMP) of radiopharmaceuticals in Europe and the US

Document	Content	References
Directive 2001/83	General principles of and guidelines for GMP	[18]
Eudralex vol. 4, annex 1: manufacture of sterile medicinal products	Details on GMP of sterile products for medicinal use	[19]
Eudralex vol. 4, annex 3: manufacture of radiopharmaceuticals	Details on GMP of radiopharmaceuticals	[19]
Eudralex vol. 4, annex 11: computerised systems	Details on GMP and validation of computerized systems	[19]
Eudralex vol. 4, annex 13: investigational medicinal products	Details on GMP for drugs and radiopharmaceuticals in clinical trials	[19]
FDA 21 CFR part 212	Details on cGMP (current GMO) for clinically used PET drug	[22]
FDA guidance: PET drugs—cGMP	Methods and procedures for production of PET drugs	[23]
USP chapter <823>	Requirements for compounding of research PET radiopharmaceuticals	[24]
USP chapter <797>	Requirements for dispensing clinical PET radiopharmaceuticals	[24]

in Annex 11 (computerized systems) and Annex 15 (qualification and validation). Since these rules and guidelines do not distinguish between the production of a few millilitre of a formulated radiopharmaceutical for a single or only a few patients and the production of several 100 kg of a drug by the pharmaceutical industry, PET centers are struggling to comply with the increasing demands and frequently changing GMP rules.

The EDQM is the organ of the European Council responsible for the European Pharmacopeia, which provides the quality standards for pharmaceutical and radiopharmaceutical preparations [20]. Over the years, several monographs on radiopharmaceuticals for PET, SPECT and endoradiotherapy have been released and published [21] (see Tables 1, 2). These monographs address specific characteristics of radiopharmaceuticals labeled with short-lived radionuclides as well as corresponding quality control procedures. Similar guidelines and documents have been published by the United States Federal Drug Administration (FDA) [22–24]. A more detailed discussion of the regulations and legislation of radiopharmaceuticals for human use is given by Decristoforo and Schwarz [25].

Typical quality control procedures in a clinical radiopharmacy

For quality control (QC) purposes (see Table 2), three samples of the final product are typically taken under laminar flow or sterile conditions (class A): (a) approx. 500 µl for sterility tests, (b) approx. 500 µl for general quality control purposes (see below) and (c) approx. 1 ml as a reference sample (retained sample which is stored for at least one year).

Sterility and endotoxin testing

One example of a QC criterion specific for short-lived radiopharmaceuticals is the allowance to release these radiopharmaceuticals before completion of all test, in particular of tests (such as sterility tests) that are not compatible with the short half live. In these cases, sterilization of the final product or final sterile filtration (0.22 µm filter) plus performance of a filter integrity test (e.g., bubble point test) prior to release is required. Former time-consuming endotoxin tests have been substituted by modern and rapid automated endotoxin testers that are able to provide valid results within a few minutes.

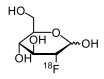
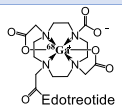
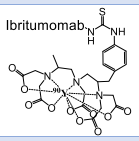
Appearance

The ‘appearance’ test is a general test to be carried out on all products (generally: liquids ready for injection with a volume of 8 to ca.15 mL) to confirm the absence of visible particles, turbidity or color. For this purpose, the vial is inspected by means of tweezers through a lead window of a typical U shape shielding where the samples taken for quality control are placed (in the QC lab) during the QC procedure.

Identity, chemical purity and radiochemical purity

Radio-HPLC is probably the most important and most often used QC-procedure. With radio-HPLC, several fundamental characteristics can be determined (although in some cases not completely): (a) the incorporation of the radioisotope into the correct molecular species (the ‘identity’ of the radiopharmaceutical, e.g., radiometallated peptides or antibodies, ^{18}F-labelled small molecules etc.), (b) the presence of other radiolabelled species that do not co-elute with the product; e.g., other small molecules labelled with ^{18}F, protein fragments or oxidized radiometallated peptide species formed by radiolysis during the production etc. (radiochemical purity), and (c) the presence of non-labelled organic contaminations, e.g., residual precursor, fragments, elimination products, residual reagents etc. (chemical purity). Obviously, a broad range of HPLC columns is necessary to be able to analyze radiopharmaceuticals with highly variable physicochemical characteristics: (a) RP18 reversed phase columns for almost all ^{18}F- and ^{11}C-compounds, (b) anion exchange chromatography for e.g., the analysis of ^{18}F-FDG or ^{18}F-fluoride solutions (or cation exchange chromatography and ion pair chromatography for others), or (c) size exclusion chromatography for proteins such as radioiodinated albumin or proteins. In combination with these columns, either UV detectors, electrochemical or refractive index detectors (for FDG) are commonly used. However, some data cannot be acquired by radio-HPLC. Since an HPLC profile only reflects the mass profile of compounds eluted from the column during a dedicated time span, it is often unclear whether additional compounds that are retained more strongly on the column or even adhere to the column material are not susceptible of quantitative analysis or converted during the HPLC analysis. A prominent example it the radio-HPLC analysis [^{18}F]FDG, where non-hydrolyzed (still acetyl protected) tetra-acetyl-2[^{18}F]glucose or partly hydrolyzed products are never detected, even when they are present in the final product: since the mobile phase used for the strong basic anion-exchange chromatography of small carbohydrates is 0.1 M NaOH, the protecting groups (acetyl groups) are cleaved during the radio-HPLC analysis of [^{18}F]FDG thus not allowing to quantify the presence of only partly hydrolyzed product. In this context and as a general second chromatography method, radio-TLC instruments are commonly installed in modern radiopharmacies.

Table 2 Tabular representation of some selected monographs from the European Pharmacopeia, V.8.0

		Appearance	Radiochemical Purity	Radionuclide Identity	Radionuclidic purity	pH	Impurity	Specialty
Method		Visual test	a) HPLC b) TLC	a) γ –spectrometry b) Half-life c) HPLC	a) Immediate γ-spectrometry b) γ -spectrometry after > 24h	Potentiometric detection	HPLC / Spot Test / UV/VIS	
Fludeoxyglucose (^{18}F) Injection # 01/2014:1325		Clear, colorless or slightly yellow solution	a) ≥ 95 % ^{18}F FDG / ≤ 10% of hydrolyzed derivatives b) ≤ 5% due to free ^{18}F and partially or fully acetylated derivatives	a) 511 keV γ´s and evtl. sum peak at 1,022 keV b) 105–115 min c) R_t is similar to reference	a) ≥ 99.9% ^{18}F b) ≤ 0.1% impurities	4.5 – 8.5	Omitted if impurities are not used /cannot be formed during the production process	-
Method		Visual test	HPLC	a) γ-spectrometry b) Half-life	γ-spectrometry	Potentiometric detection	Color intensity test for a) Ammonium b) Nitrates	-
Water (^{15}O) Injection # 01/2008:1582	$H_2{}^{15}O$	Clear, colorless liquid	≥ 99% ^{15}O Water	a) 511 keV γ´s and evtl. sum peak at 1,022 keV b) 1.9 – 2.2 min	≥ 99% ^{15}O	5.5 – 8.5	a) ≤ 10 ppm b) ≤ 10 ppm	-
Method		Visual test	TLC	a) γ-spectrometry b) Half-life c) Silver nitrate test d) Retention on SCX	a) Immediate γ-spectrometry b) 511 keV γ's after 48h decay	Indicator strip	Atomic absorption spectrometry for a) Fe ; b) Zn	-
Gallium (^{68}Ga) Chloride Solution for Radiolabeling # 07/2013:2464	$^{68}GaCl_3$	Clear, colorless solution	≥ 95 % ^{68}Ga	a) 511 keV γ´s and evtl. sum peak at 1,022 keV b) 62–74 min c) Precipitate is formed d) ≥ 90% are retained on SCX	a) ≥ 99.9% ^{68}Ga b) ≤ 0.001% ^{68}Ge	max. 2.0	a) ≤10µg/GBq b) ≤10µg/MBq	-
Method		Visual test	a) HPLC b) TLC	a) γ-spectrometry b) Half-life	a) Immediate γ-spectrometry b) 511keV γ's after 48h decay	Indicator strip	HPLC for DOTA-TOC and metal complexes of DOTA-TOC	GC for a) Ethanol content TLC for b) HEPES Content
Gallium (^{68}Ga) Edotreotide Injection # 01/2013:2482		Clear, colorless solution	≥ 91 % ^{68}Ga-peptide a) ≤ 2% ^{68}Ga(III) b) ≤ 3% colloidal ^{68}Ga	a) 511 keV γ´s and evtl. sum peak at 1,022 keV b) 62–74 min	a) ≥ 99.9% ^{68}Ga b) ≤ 0.001% ^{68}Ge and impurities	4.0–8.0	≤50 µg	a) Ethanol ≤ 10% V/V, ≤2.5 g/administration b) HEPES ≤ 200 µg/V
Method		Visual test	TLC	a) β-radiation mass absorption coefficient b) β-spectroscopy	TLC / Scintillation Counter	Potentiometric detection	-	-
Yttrium (^{90}Y) Ibritumomab Tiuxetan Injection # USP 29-NF24		Clear, colorless solution	a) ≥ 95% of ^{90}Y	a) Within 5% of standard reference b) E_{max} at 2280 keV	Total activity of ^{90}Sr ≤ 740 KBq per 37 GBq of ^{90}Y	5.5 – 7.5	-	-
Method		Visual test	Paper chromatography	a) γ-spectrometry	a) Preliminary γ-spectrometry b) Definitive γ-spectrometry	Potentiometric detection	Color intensity test for Aluminum	
Sodium pertechnetate (^{99m}Tc) Injection (Non-Fission) # 01/2005:0283	$Na[^{99m}TcO_4]$	Clear, colorless solution	≥ 95% ^{99m}Tc Pertechnetate	a) 140 keV γ´s	a) 740 keV γ's response of 37 MBq test solution < 37 KBq ^{99}Mo reference b) ≤ 0.1% ^{99}Mo and ≤0.01% other radionuclides of total radioactivity	4.0 – 8.0	≤ 5ppm	For all further radiopharmaceutical preparations from sodium pertechnetate ^{99m}Tc injection (fission or non-fission), no test for radionuclidic purity is necessary
Method		Visual test	HPLC	γ-spectrometry	a) Immediate γ-spectrometry b) γ-spectrometry	Potentiometric detection	HPLC for [^{123}I]Iodate ion	Production
Sodium Iodine (^{123}I) Injection # 01/2008:0563	$Na^{123}I$	Clear, colorless liquid	≥ 95 % [^{123}I]Iodide of total radioactivity	Obtained spectrum does not differ significantly from reference. 159 keV γ´s accompanied by X-ray of 27 keV	a) ≥ 99.65% ^{123}I b) After sufficient decay of ^{123}I, no radionuclides with a half-life longer than ^{125}I are detected	7.0 – 10.0	≥ 95 % [^{123}I]Iodide of total radioactivity	Obtained by proton irradiation of Xenon enriched in ^{124}Xe followed by decay of ^{123}Xe. No carrier iodide added

* Each monograph demands testing of bacterial endotoxins to ensure <175/V IU/V

** Each monograph demands testing of sterility

*** Residual solvent, if demanded, is typically analyzed by gas chromatography

For ^{99m}Tc kit preparations, only approved ^{99m}Tc generators and approved lyophilized kits are used. For such kit preparations, radio-TLC (or paper chromatography) represents the primary method for quality control, besides being used as a second additional chromatographic analysis for other radiopharmaceuticals. A variety of commonly used mobile phases that guarantee optimal separation of the labeled product and radioactive contaminations and thus provide valid QC results have been investigated and published.

Radionuclide identity and radionuclide purity (radionuclidic impurities)

Radionuclide identity and radionuclide purity (radionuclidic impurities) are investigated by means of γ-

spectrometry. Whereas the determination of the characteristic γ-emissions clearly indicates the presence of most of the SPECT (^{123}I, ^{111}In, ^{99m}Tc etc.) and therapeutic radioisotopes (^{177}Lu, ^{131}I, ^{90}Y etc.), PET isotopes can be identified as such by the presence of a 511 keV (and a sum peak at 1022 keV), but cannot be distinguished from one another. Thus, determination of the half-life over a period of at least three half-lives of the respective radionuclide of interest need to be carried out, typically by linear regression of data obtained with a γ-spectrometer or a sufficiently sensitive dose calibrator. In some cases it is not necessary to carry out this test for all production runs. Thus, for example, only one initial determination of the half life of ^{18}F-fluoride produced by irradiation of a new batch of [^{18}O]H_2O is required. Similarly, the identity and purity of $^{68}Ga^{3+}$ ($T_{1/2} = 68$ min) eluted from a ^{68}Ge/^{68}Ga-generator is investigated approx. once a month. For this purpose, the γ-spectrum and the decay of a defined sample of the generator eluate is measured immediately after elution (^{68}Ga) and 48 h after elution (on the same sample: ^{68}Ge-breakthrough) [18]. Another important example is the presence of up to 0.4 kBq ^{177m}Lu ($T_{1/2} = 161$ days) per MBq ^{177}Lu ($T_{1/2} = 6.7$ days) at the end of neutron irradiation when ^{177}Lu is produced by the ^{176}Lu (n, γ) ^{177}Lu process, since these long lived ^{177m}Lu contaminations can cause significant problems when mixed with other typically used therapeutic radionuclides, such as ^{131}I, in decay tanks of hospitals [16]. In vivo problems (dosimetry) with small ^{177m}Lu contaminations in ^{177}Lu-radiopharmaceuticals have not been reported so far.

Volume, radioactivity concentration, shelf life

The overall volume of a final radiopharmaceutical ready for injection is also important. In accordance with national laws, radiopharmaceuticals are treated as drugs; thus the effect (the PET image quality) of the medication (the PET radiopharmaceutical) must be ensured until the end of the shelf life. Consequently, the shelf life is defined as the time point when the radioactivity of the entire product volume with the minimum specified activity concentration (at the end of production) has to be injected into one patient to obtain a PET image of suitable quality. In addition, it has to be demonstrated that the product meets all specifications, i.e., the criteria defined for the radiochemical purity (affected by radiolysis over time) at the end of the shelf life. If radiolysis is fast, the shelf life is determined by the radiochemical purity. As the kinetics of radiolysis have to be investigated during the validation process of each radiopharmaceutical, the maximum radioactivity concentration (e.g., GBq/ml) is determined by the highest activity concentration tested for radiolysis in these validation runs.

Residual solvents

Since the maximum volume (typically between about 8–15 ml) also determines the maximum injected dose of e.g., residual solvents, such as ethanol from solid phase extraction procedures (e.g., FDG-TUM: 1200–2500 µg/ml; to ensure radiolytic stability, lower limit must be fulfilled; see Table 3) or acetonitrile (limit in FDGTUM: 270 µg/ml) from ^{18}F-fluorinations etc. to be injected into a patient at the end of the shelf life, maximum doses (e.g., in mg/V; *V* entire volume) are also specified for typical impurities (see Table 1). As demonstrated by the use of V for the specification of the maximum injectable dose for each impurity, the overall volume must also be reproducible and within a well-defined and suitably narrow range.

pH and osmolality

The determination of the pH is also routinely carried out. Although not mentioned in the specific monographs, the determination of the osmolality (human plasma osmolality: 290 m Osm/l, range: 285–310 mOsm/l; former limit for FDG-TUM: 350–550 mOsm/kg) is also carried out by some radiopharmacies.

As a typical example, Table 3 summarizes the release criteria of FDG-TUM (FDG with market authorization produced at the Technische University Munich). Apart from the methods, two columns (old/new specifications) are listed. The 'old' specifications were established in 2000 as part of the approval process for market authorization. At that time, FDG was produced from [^{18}F]fluoride generated by means of a RDS cyclotron, and the synthesis was carried out by a Siemens CTI CPCU-module. To meet the continuously increasing GMP demands and to be able to use a new cyclotron (GE PETtrace 800; installed in 2014) and a new FASTlab-module for the approved FDG-TUM production process, new validation runs were carried out and new specifications and release criteria were compiled. The latter was accomplished in close interaction with the local authorities.

As demonstrated in Table 3, the osmolality test was omitted, and some specifications were modified (e.g., determination of fluorodeoxy-mannose (FDM) instead of chlorodeoxy-glucose (ClDG), since in the new process HCl deprotection of the tetra-acetylated mannose triflate precursor was substituted by alkaline hydrolysis). In addition, frequencies of tests (e.g., radionuclide identity and radionuclide impurities only once per month and once for each new [^{18}O]H_2O batch) or acceptable ranges (pH) etc. were changed, demonstrating that GMP (or cGMP; current Good Manufacturing Practice, as used in the US) is not an inflexible and rigid system of guidelines, but a dynamic

Table 3 Specifications/release criteria for [^{18}F]FDG produced at the TUM (Technische University Munich, Germany (FDGTUM with market authorization)

	Tests	Old			New	
		Method	Specification		Method	Specification
P	Appearance	Visual	Clear, colorless solution	P	Visual	Clear, colorless solution
P	Volume of single dose	Balance	≤15 ml	P	Balance	≤15 ml
P	pH-value	pH meter	6.5–8.0	P	Indicator strip	4.5–8.5
P	Radioactivity concentration	Dose calibrator/ balance	≥208 MBq/ml ≤1665 MBq/ml	P	Dose calibrator/ balance	≥208 MBq/ml ≤1665 MBq/ml
P	Radioactivity and radioactivity volume, concentration of single dose	Dose calibrator	Meets customer requirements	P	Dose calibrator	Meets customer requirements
P	Radiochemical identity	Radio-HPLC	R_f = 97–103% of reference	P	Radio-HPLC	R_f = 97–103% of reference
P	Radiochemical purity	Radio-HPLC	≥98%	P	Radio-HPLC	≥98%
P	Radiochemical impurities	Radio-HPLC	Fluoride ≤1%; signal@ 2.8 min: ≤0.25%; signal@4.7 min: ≤0.5%; signal@15.5 min: ≤0.25%	P	FDM + FD FDM	≥95% ≤10%
P	Content of acetonitrile	GC	≤100 μg/ml	P	GC	≤270 μg/ml
P	Content of D-glucose	HPLC	≤500 μg/ml	P	HPLC	≤500 μg/ml
P	Content of acetate	HPLC	≤1000 μg/ml	P	HPLC	≤720 μg/ml
P	Content of ClDG	HPLC	≤33 μg/ml	P	HPLC	Cancelled
P	Content of FDG	HPLC	≤25 μg/ml	P	HPLC	≤33.3 μg/ml
P	Content of FDM	HPLC	–	P	HPLC	≤33 μg/ml
A	Radiochemical purity	Radio-TLC	≥96%	P	Radio-TLC	≥95%
A	Radiochemical impurities	Radio-TLC	Fluoride @R_f ≤ 0.2 and R_f ≥ 0,6: <4%	P	Radio-TLC	Sum of impurities <5%
A	Radionuclidic identity	γ-spectrometry half live (1)	Signal@0.511 MeV 105–115 min	P	γ-spectrometry half live[a]	Signal@0.511 MeV 105–115 min
A	Radionuclidic purity	γ-spectrometry	Overall ^{18}F activity: ≥99%	P	γ-spectrometry	Overall ^{18}F activity: ≥99%
A	Radionuclidic impurities[a]	γ-spectrometry	^{55,56,57,58}Co; ^{54,58}Mn; ^{95,96}Tc; ^{107,109}Cd; not detectable	A	γ-spectrometry[a]	^{55,56,57,58}Co; ^{54,58}Mn; ^{95,96}Tc; ^{107,109}Cd; not detectable
A	Specific activity	Radio-HPLC	>3.8 GBq/μmol	P	Radio-HPLC	>3.8 GBq/μmol
A	Content of TBA/Kryptofix	Radio-HPLC	<0.1 mg/ml	P	Kryptofix (spot test)	≤50 μg/ml
A	Osmolality	Freezing point depression	350–550 mOsm/kg	P	Cancelled	Cancelled
A	Endotoxines	Endpoint chromog. LAL assay	<11.6 EU/ml	P	Automated LAL test	<11.6 EU/ml
A	Sterility	Growth	Sterile	A	Growth	Sterile

Old release criteria from 2000 to 2015 (RDS cyclotron, Siemens CTI CPCU-module); *new* release criteria (GE PETtrace 800, FASTlab-module)

[a] Once per month and once for each new [^{18}O]H_2O batch

A Test must be completed prior to release, *P* Test can be completed after release

and changing system that is continuously adapted to the current state of knowledge and experiences.

Outlook

After a decade of outstanding technical achievements in molecular imaging, this expertise is now expected to add more momentum and innovation to the advancement of radiopharmaceuticals for molecular imaging and radionuclide therapy. However, this innovation pressure is accompanied by continuously rising demands and legal requirements on clinical GMP production of radiopharmaceuticals. It will be of utmost importance to establish a new research focus that allows to suitably address this topic of continuously growing importance. In view of the cost explosion in that area, appropriate and sustainable strategies must be defined, and solutions need to be developed and elaborated. Without such perspectives and solutions, the transfer of new diagnostic and therapeutic radiopharmaceuticals into clinical application—the final objective of translational radiopharmaceutical development—will in the future only be possible with considerable financial expenditure.

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