Chapter

Radiopharmaceutical Precursors for Theranostics

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Abstract

Due to the complex nomenclature used in various regulations and guidance documents, the understanding of radiopharmaceutical precursor's definition might be challenging. Depending on the context it could be interpreted as the substance which becomes a radiopharmaceutical after radiolabeling with a radionuclide of choice or a radionuclide which is used for radiolabeling of that substance. In this Chapter we present and discuss the requirements for precursors which are used in the preparation of theranostic radiopharmaceuticals, in particular for preparation of new radiopharmaceuticals for clinical trials within the EU. In discussion on the available methods for assessing the quality of radiopharmaceutical precursors and on the specified limits the reference to Ph. Eur. is made. Since the EANM guidelines for in-house preparation of radiopharmaceuticals also specify the need for testing the quality of radiopharmaceutical precursors, information provided herein might help the radiopharmacist working on the development of new theranostic agents to adequately define identity, strength, quality, purity and stability of the final radiopharmaceutical preparation.

Keywords: radiopharmaceutical precursors, radionuclide precursor, chemical precursor, peptides, IMPD, clinical trials

1. Introduction

This chapter deals with regulatory considerations related to radiopharmaceutical precursors within Europe. Outside, different aspects may apply, with the exception of certain harmonized documents. Radiopharmaceuticals are considered a safe class of medicinal products. Due to the small chemical quantities administered they are not expected to exhibit any measurable pharmacological effect [1]. However, since they are radioactive, the rules for minimizing the risk associated with the use of ionizing radiation to the patients and to the personnel must be observed. Depending on the chemical and physical properties, radiopharmaceuticals are used in major clinical areas for diagnostics and/or therapy [2]. As defined by the European Pharmacopeia (Ph. Eur.) general monograph (0125) *radiopharmaceutical preparations or radiopharmaceuticals* are medicinal products which, when ready for use, contain one or more radionuclides (radioactive isotopes) included for a medicinal purpose [3]. Importantly, they can also have the form of kits for radiopharmaceutical preparation, radionuclide generators and radionuclide precursors.

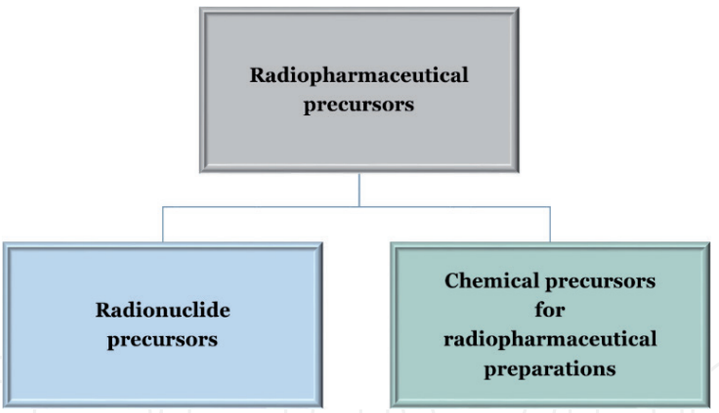

Figure 1.
Radiopharmaceutical precursors according to Ph. Eur.

For the latter it is understood that they are not used in patients as such but only after attaching them to the suitable pharmaceutical vector. Although according to Ph. Eur. monograph (0125) *radionuclide precursor* is any radionuclide produced for radiolabeling of another substance prior to administration, and according to Ph. Eur. general monograph (2902) the substance, which is used as such vector, is defined as a *chemical precursor for radiopharmaceutical preparations* [4], the term *radiopharmaceutical precursor* is used interchangeably for either of the two above defined precursors (**Figure 1**).

2. Current regulatory framework

Given the complex nomenclature used in various regulations and guidance documents, the understanding of radiopharmaceutical precursor's definition might be challenging. Depending on the context it could be interpreted as the substance which becomes a radiopharmaceutical after radiolabeling with a radionuclide of choice or a radionuclide which is used for radiolabeling of that substance. Therefore, the quality requirements and test methods specifications of precursors for use in preparation of theranostic radiopharmaceuticals can be discussed only in the light of current regulatory framework.

The preparation and use of radiopharmaceuticals are regulated by number of directives, regulations and rules. These documents may be classified with respect to the status of radiopharmaceutical preparation:

1. radiopharmaceuticals with marketing authorization (MA), regulated by:
   - Directives: 2001/83/EC [5], 2003/94/EC [6], 2004/27/EC [7];
   - GMP guidelines and annexes [8];
2. radiopharmaceuticals to be used in clinical trials (CT), regulated by:
   - Directives: 2001/20/EC [9], 2003/94/EC [6], 2005/28/EC [10]
   - and soon to be replaced by Regulation EU No 536/2014 [11];
3. unlicensed radiopharmaceuticals extemporaneously (just before use) prepared, not for CT [12, 13].

Radiopharmaceuticals with marketing authorization (MA) meet the requirements of GMP Annex 3 (Manufacture of Radiopharmaceuticals) [8] and EMA Guideline on Radiopharmaceuticals [12]. For the small scale preparation of radiopharmaceuticals outside the marketing authorization the guide of the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S) [14], the Guidelines on Good Radiopharmacy Practice (CRPP) issued by the Radiopharmacy Committee of European Association of Nuclear Medicine (EANM) [13] and the Chapter 5.19. Extemporaneous preparation of radiopharmaceutical preparations of the Ph. Eur. [15] are setting standards for good practices.

The translation of new radiopharmaceuticals from the preclinical stage into clinical trials requires appropriate quality assessment essential to ensure efficacy and safety of both drug substance and drug product [16, 17]. The specific regulatory framework for the use of radiopharmaceuticals in clinical trials has been established in Europe [9, 11, 18]. From the radiopharmaceutical development perspective, the essential step is the preparation of an Investigational Medicinal Product Dossier (IMPD). This document includes information related to the chemical and pharmaceutical quality of the drug substance and drug product, as well as non-clinical data related to pharmacology, pharmacokinetics, radiation dosimetry and toxicology [19]. IMPD contains two main sections related to the production and quality control of the radiopharmaceutical: the drug substance (the active pharmaceutical ingredient, or API) and the drug product.

An *active pharmaceutical ingredient (API)* is defined as any substance or mixture of substances intended to be used in the manufacture of a drug product. Such substances are intended to provide pharmacological activity or other direct effect in the diagnosis as well as treatment of disease or to affect the structure and function of the body. Radiopharmaceutical preparations are often formulated using predefined radionuclide precursors and chemical precursors. If such a preparation does not need a purification step prior to its administration to the patient, both precursors used in the synthesis are considered to be an API in the drug substance part of IMPD. This in particular applies to precursors for theranostic applications where a radiometal is used to radiolabel a vector targeting the receptor, e.g. peptide. On the other hand, chemical precursors used in the manufacture of radiopharmaceuticals, which are purified after the radiolabeling process, are defined as API starting material (e.g. chemical precursors for most F-18 and C-11 PET radiopharmaceuticals).

The manufacture of APIs should be carried out following general GMP requirements. In a GMP-based system, all processes are defined, systematically reviewed, and shown to be capable of consistently providing medicinal products of the required quality and complying with their specifications [20]. Written and approved protocols specifying critical steps, acceptance criteria, must be in place. Process validation is a crucial part of GMP, meaning that all critical steps of manufacturing processes as well as significant changes to these processes are validated. It should be noted that the requirements for validations differ depending whether marketing authorization, clinical trials or in-house preparation of radiopharmaceuticals are planned (see also **Figure 2**.) [21]. The qualification and validation aspects related to the small-scale "in house" preparation of radiopharmaceuticals are covered in the EANM guidance [22].

In the process of IMPD preparation the prime challenge is to establish quality specifications for radiopharmaceutical precursors. They are supposed to comprise a set of tests that are necessary to confirm identity, purity and strength of the drug substance. Issues under consideration are the definition of release criteria, analytical procedures and especially their validation. Main references to address these issues are the European Pharmacopeia and guidance provided by the International Conference

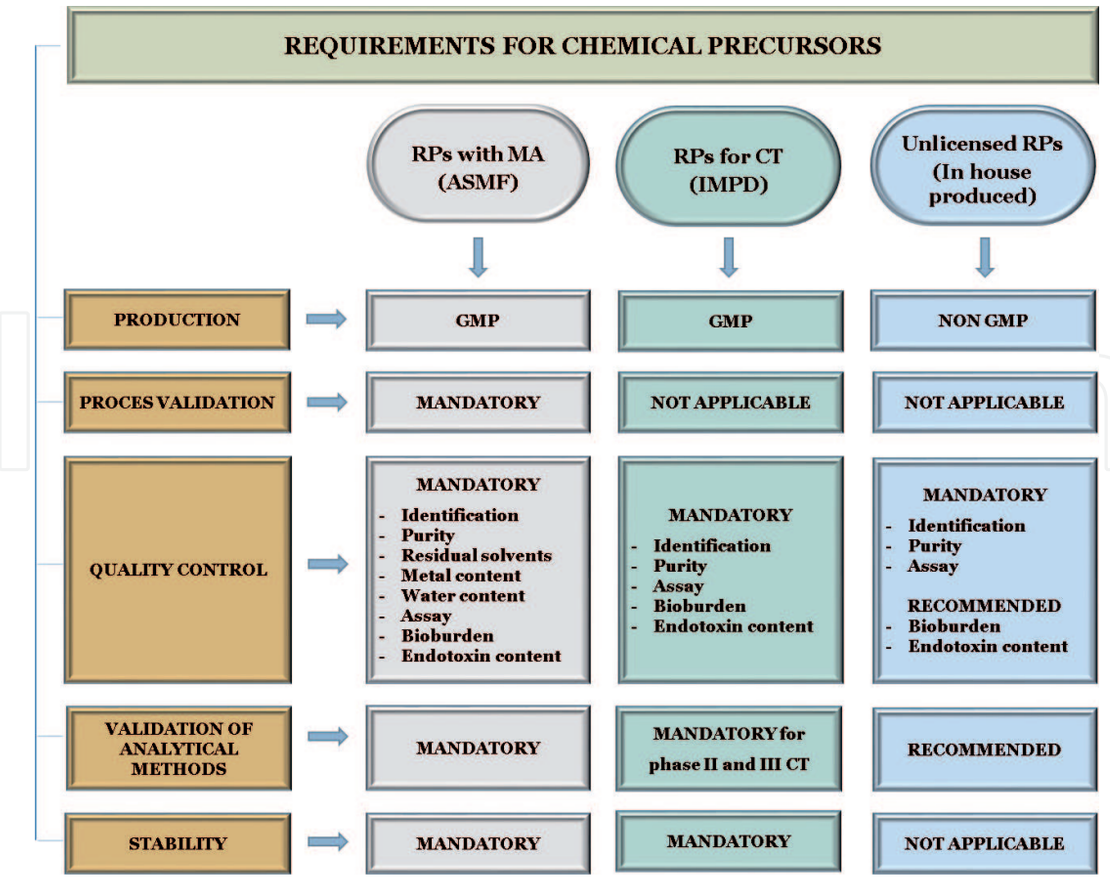

Figure 2.
Requirements for chemical precursors used in preparation of radiopharmaceuticals depending on their regulatory status.

on Harmonization (ICH). Ph. Eur. provides general requirements for quality control of radiopharmaceutical precursors, in addition, a number of monographs for individual radiopharmaceuticals and chemical precursors are available in the Ph. Eur.

The use of analytical methods described in the pharmacopeia allows to reduce the work load related to analytical method validation. This does not mean that a pharmacopeia method may be implemented without any preliminary testing and verification. As a minimum, the most critical parameters should be verified, depending on the intended method. If no pharmacopeia monograph exists, analytical methods need to be fully validated. As stated by the general reference document issued by ICH the objective of validation of an analytical procedure is to demonstrate that it is suitable for its intended purpose [23]. To validate an analytical method, the following characteristics may be considered: specificity, accuracy, linearity range, precision (repeatability and intermediate precision), limit of detection (LOD), limit of quantitation (LOQ) and robustness. Recently, recommendations for the validation of analytical methods which are specific for radiopharmaceuticals has been published by EANM [24].

3. Chemical precursors for radiopharmaceutical preparations

Chemical precursors for radiopharmaceutical preparations, are non-radioactive substances obtained by chemical synthesis for combination with a radionuclide in contrast to precursors manufactured using substances of human or animal origin [4].

The quality specification for chemical precursors is built upon three elements: exact methods, test limits and selection of reference standard. Pharmacopeia monographs

comprise a set of critical attributes categorized into three subdivisions: identity, tests (related substances, residual solvents, metal catalyst or metal reagent residues, microbial contamination, bacterial endotoxin) and assay of the active substance. To ensure the appropriate quality, reference substances (like primary standards e.g. Ph. Eur. Chemical Reference Substance, CRS, or Pharmaceutical Secondary Standard, PSS) are used as a standard in an assay, identifications, or purity test. CRS or PSS are often characterized and evaluated for its intended purpose by additional procedures other than those used in routine testing [25].

For in-house prepared radiopharmaceuticals the confirmation of the chemical identity and purity of the precursor are the minimum quality control required, in order to qualify the material for subsequent clinical radiolabeling. Additional testing may apply if necessary for the specific process. For example, testing of trace metals content may not be necessary when the material will be subsequently radiolabeled with halogens, but is absolutely critical when the material is intended for labelling with radiometals [26].

To bring a novel radiopharmaceutical into the clinic it is needed that specific quality requirements for the radiopharmaceutical precursor are established, the range of testing would depend on their status and/or intended use. It is worth noting that for Phase I clinical trials full analytical validation is not necessary (only method suitability should be confirmed) [21]. While analytical methods used to evaluate a batch of API for clinical trials may not yet be validated, they should be scientifically sound [27].

There are some specific requirements for the large-sized molecules (e.g. proteins or monoclonal antibodies) as radiopharmaceutical precursors [28]. Monoclonal antibodies are immunoglobulins (Ig) with a defined specificity derived from a monoclonal cell line. Their biological activities are characterized by a specific binding characteristic to a target ligand (e.g. antigen) and they may be generated by recombinant DNA (rDNA) technology, hybridoma technology, B lymphocyte immortalization or other technologies. Generally, when chemical precursors are manufactured using substances of human or animal origin, the requirements of Ph. Eur. chapter 5.1.7. Viral safety [29] and the general monograph Products with risk of transmitting agents of animal spongiform encephalopathies (1483) [30] apply.

Stability testing is part of the chemical precursor's characterization. Detailed requirements for carrying out stability studies are included in the ICH guideline Q1A (R2) [31]. The purpose of stability testing is to provide evidence on how the quality of a substance varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light, and to establish a re-test period and recommended storage conditions. Stability studies should be carried out on at least three batches and include testing parameters of the chemical precursor that are susceptible to changes during storage and may affect quality, safety and efficacy (e.g. chemical purity and/or assay). The validated analytical methods should be used in these tests. For method validation, it is essential to investigate degradation products and establish degradation pathways under stress conditions (e.g. heat, humidity, light, acid/base hydrolysis and oxidation).

4. Peptides as precursors for radiopharmaceutical preparations

4.1 General consideration

Peptides are an emerging class of compounds that have application in theranostics of several diseases, mainly in cancer [32–36]. These chemical precursors are positioned between the classic small organic molecules and the high

molecular weight biomolecules. The interest of the scientific community for peptide drugs has been continuously growing. Currently, more than 60 peptide-based pharmaceuticals are marketed, over 150 peptides are in active clinical trials and estimated 500 more are in preclinical stages of development [37, 38]. Chemically, peptides have poly-amino acids structure ranging from 3 to 100 amino acids (less than 10 kDa) linked by a peptide (amide, –CONH–) bond, and are lacking a tertiary structure. From the biological point of view, peptides are important regulators of growth and cellular functions in normal tissue and tumors. They can act as cytokines, chemokines, neurotransmitters, hormones and growth factors. Generally, they offer many advantages over other groups for radiopharmaceutical applications. Peptides demonstrate high receptor specificity and selectivity, as well as binding affinity, good tissue penetration and favorable pharmacokinetic profiles. Most of them is characterized by low toxicity and immunogenicity [39, 40]. Their compact size results in rapid targeting and blood clearance. As a consequence low nonspecific uptake in non-targeted tissues and high target-to-background ratios are achieved. Moreover, peptides can be easily chemically synthesized in high purity, modified and stabilized to obtain optimized pharmacokinetic parameters. These all attributes together with ability to attach different chelating agents, prosthetic group and availability of various bioconjugation techniques make peptides an important target platform for theranostic radiopharmaceuticals [41, 42].

Peptide-based radiopharmaceuticals were introduced into the clinic more than three decades ago [43]. Since that time, several theranostic radioligand platforms are used for diagnosis and peptide receptor radionuclide therapy (PRRT) of different cancer types. In this concept, peptide analogs directed against somatostatin receptors (SSTR) play a crucial role [44]. The most prominent example of the theranostic pair of radiolabeled peptides are DOTA-conjugated SSTR agonist DOTA-(D-Phe^{1}, Tyr^{3}, Thr^{8})-octreotate (DOTA-TATE) labeled with ^{68}Ga and ^{177}Lu (**Figure 3**). The marketing authorization of NETSPOT® ([^{68}Ga]Ga-DOTATATE) in 2016 and LUTATHERA® ([^{177}Lu]Lu-DOTATATE) in early 2018 [45] encouraged the research in this field to develop improved radiolabeled peptides targeting other receptor/antigen families, exemplified by the prostate specific membrane antigen (PSMA) [46], gastrin-releasing peptide receptor (GRPr) [47] and cholecystokinin-2 receptor (CCK_2R) [48, 49]. Some of these peptides are currently under clinical investigation.

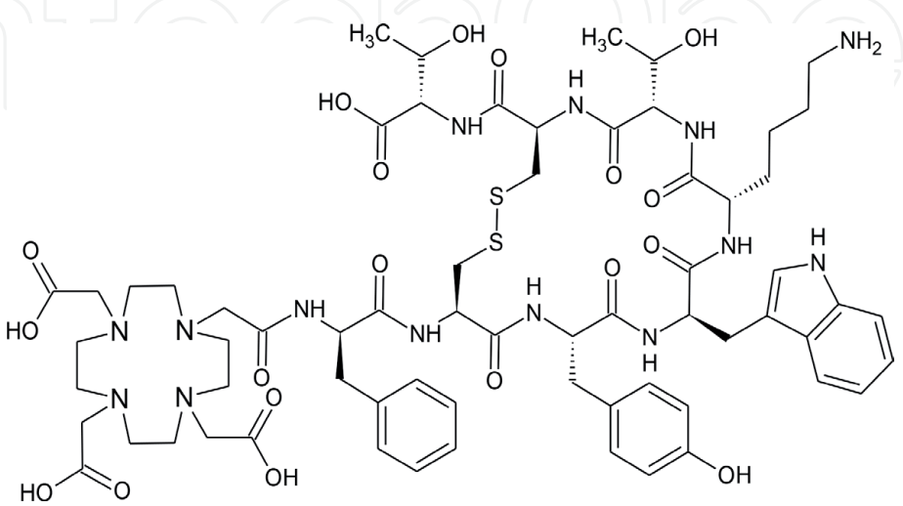

Figure 3.
Structure of DOTA-TATE for labelling with theranostics pair of radionuclides: Gallium-68 (^{68}Ga) and lutetium-177 (^{177}Lu).

4.2 Quality aspects

Peptides as precursors for radiopharmaceutical preparations, similarly to other chemical precursors, require adequate specification as a part of their quality assurance in order to demonstrate the safety and efficacy of the final radiopharmaceutical preparation. Currently, no individual pharmacopeia monograph of peptide used as radiopharmaceutical precursors is available. Thus, the quality specification should be established according to the general requirements [4, 50]. Herein, we provide an overview of recommended methods and test limits for the characterization of peptides. The set of analytical procedures that need to be considered is presented in **Table 1**. However, it should be noted that new analytical methods and modifications to existing ones are continuously being developed and should be utilized where appropriate.

Parameters	**Typical methods**	**Typical acceptance criteria**
Characters		
- Appearance/color	Visual inspection	White or almost white powder
- Solubility	Visual inspection	Solubility in water, ethanol and dilute acid or alkali
Identification		
- Active moiety	RP-HPLC-UV	Retention time *versus* reference
	MS or	Mass spectrum *versus* reference
	NMR	NMR spectrum *versus* reference
	IR	IR spectrum *versus* reference
	AAA (GC)	AA: theoretical content ±20%
Purity tests		
- Related substances	HPLC-UV	Individual, unidentified: < 2.0% Total: ≤ 3.0%
- Residual solvents	(Headspace) GC	Acetonitrile: ≤ 0.5%
- Residual metals	AAS/ICP-AES/ICP-MS	Pt, Pd, Ir, Rh, Ru, Os, Mo, Ni, Cr, V, Pb, Hg, Cd, Tl: ≤ 0.01%
- Residual reagents	HPLC-UV/IC/GC	Trifluoracetic acid: ≤ 1.0%*
Counter-ion content	HPLC-UV/IC/GC	Acetic acid: target ±5% Trifluoracetic acid: target ±5%
Water content	Karl-Fisher	≤ 10.0%
Assay (net peptide content)	RP-HPLC-UV or CHN	≥ 75.0%
Bioburden	TAMC plate count	≤ 10^3 CFU/g for bulk ≤ 10^2 CFU per container
	TYMC plate count	≤ 10^2 CFU/g for bulk ≤ 10^1 CFU per container
Bacterial endotoxins	Gel-clot	≤ 100 IU/g for bulk ≤ 10 IU per container

**The residual TFA content is determined when AcOH or HCl are used as counter-ions.*

Table 1.
Summary of the recommended quality parameters for peptides used as radiopharmaceutical precursors.

4.2.1 Appearance

The preliminary quality evaluation of peptides is based on the visual inspection of the appearance/color and solubility. This parameter is given only for information, it is not a requirement in a strict sense. If any of the characteristics change during storage, this change should be investigated and appropriate action taken. A typical description of peptide appearance is: white to almost white, freeze-dried powder and solubility is stated in water, ethanol and dilute solutions of acids and alkali [38, 51].

4.2.2 Identification

According to the ICH Q6A guideline [25] identification testing should allow to discriminate between compounds of closely related structure which are likely to be present (e.g. peptides with altered sequences or functional groups that may be formed during the synthesis). The identification test should include combination of different procedures (mostly two) and should be specific and unequivocal. Several techniques are currently in use for confirmation of peptide identity: HPLC-UV, nuclear magnetic resonance spectrometry (NMR), mass spectrometry (MS), infrared absorption spectrophotometry (IR), amino acid analysis (AAA) or peptide sequencing [51]. The method of choice is typically HPLC-UV based on retention time by comparison with reference standard, since the separation by RP-HPLC is often utilized and the method is widely available. UV detection of peptides is realized at 210–220 nm and 250–290 nm for aromatic side chains of phenylalanine, tyrosine and tryptophan. Identification solely by a chromatographic retention time is not regarded as specific and should be complemented by spectrometric techniques. The NMR spectroscopy is the method that allows to unequivocally define the structure of a peptide in the terms of amino acid composition, sequence and chirality. Identification by NMR spectrometry is usually limited to peptides comprising up to 15 amino acids and requires complex data interpretation. For this reason NMR technique is primarily replaced by mass spectroscopy (MS). This technique provides highly accurate molecular weight information on intact molecules, which is an advantage of MS for peptide identification. The peptide molecular mass is most commonly determined by using the electrospray ionization method (ESI), which occurs through the addition or removal of protons and appears as singly or doubly charged ions. As alternative for the more sophisticated spectroscopic methods, amino acid analysis (AAA) could be considered. This technique involves the hydrolysis of the peptide (usually in acidic conditions) to its individual amino acid residues, followed by chromatographic separation and detection/quantification. The method also enables the determination of the enantiomeric purity with the use of appropriate reference standards. However, this method may not be applicable to peptides containing unnatural amino acids and/or specific chelators. The NMR and AAA as well as peptide sequencing techniques are generally used for characterization of PSS.

In the two recently published papers the identity of DOTA-TATE has been confirmed using suitable instrumental techniques; Sikora et al. [52] confirmed the identity of DOTA-TATE using three different methods: MS, IR and HPLC. Similarly, in the work by Raheem at al [53] the final product was analyzed using high resolution mass spectrometry for identification and analytical HPLC for purification; it was detected via analytical HPLC at a retention time of 9.52 min and detected by HRMS-ESI (calc m/z for $[(\text{DOTA-TATE} + 2H)/2]^+$: 718.3028, found: 718.3046 with −0.1144 ppm error).

In our experience ESI-MS in positive ionization mode was used to confirmed whether the masses of ions at m/z 1435.6 ± 1.0 $[M + H]^+$ and 718.3 ± 1.0 $[M + 2H]^{2+}$

correspond to the monoisotopic mass of peptide [M] as presented in **Figure 4**. DOTA-TATE PSS was used as reference in IR analysis. Also a gradient HPLC-UV (220 nm) served as identity test of DOTA-TATE by comparison with the reference standard (Rt ± 5.0%). The same HPLC method was used for determination of peptide purity and assay. The representative HPLC chromatograms of DOTA-TATE and DOTA-TATE PSS are given in **Figure 5**.

4.2.3 Related substances

Peptides are usually chemically synthesized using solid-phase peptide synthesis (SPPS) [54]. In this multi-stage process, amino acids are linked to each other during individual coupling steps, thus constructing the desired peptide sequence. This occurs when the carboxylic end of the sequence is covalently attached to a solid support matrix. The complexity of the peptide production process results in a greater diversity of potential impurities. Heterogenicity of the impurity profile is observed

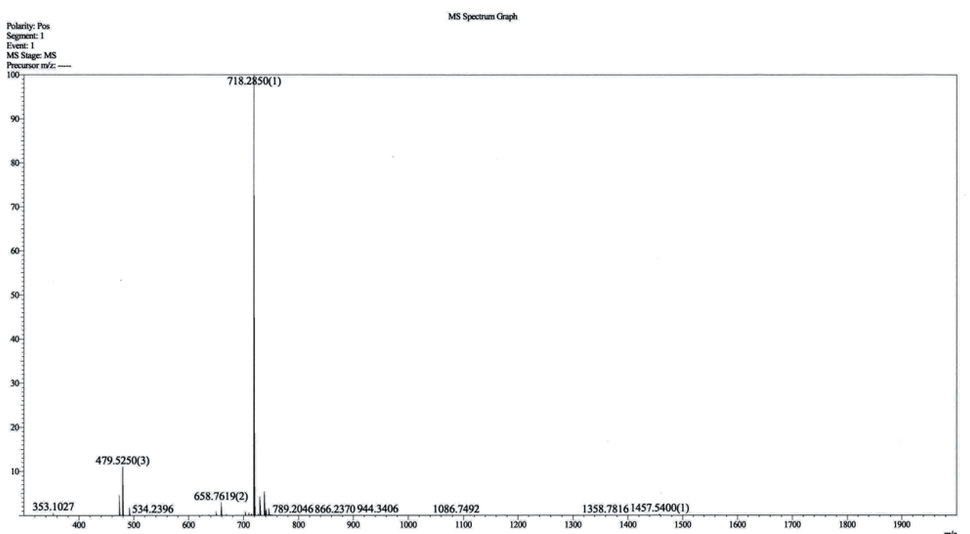

Figure 4.
ESI-MS spectrum for DOTA-TATE.

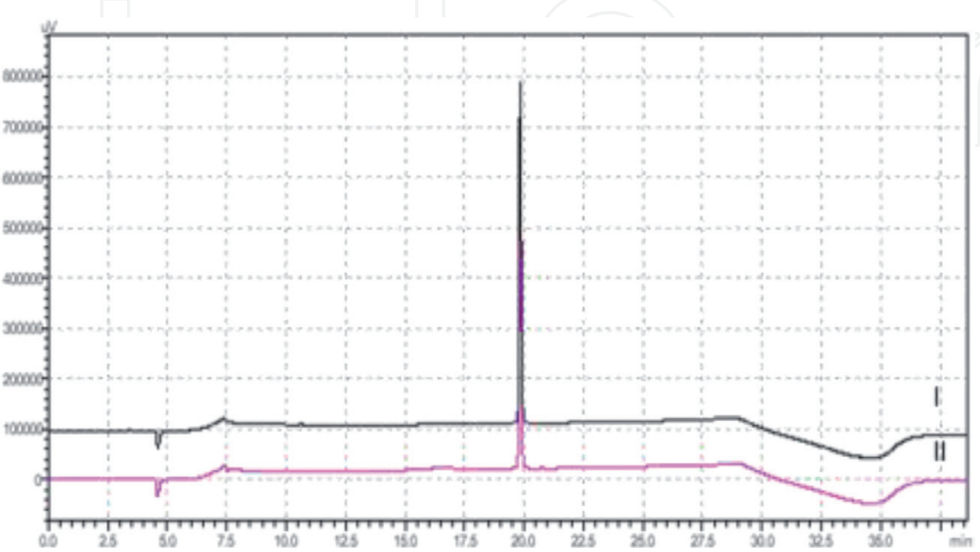

Figure 5.
HPLC-UV (220 nm) chromatograms of (I) DOTA-TATE Rt = 19.831 min and (II) DOTA-TATE PSS Rt = 19,936 min. HPLC method: Luna C18(2) column; Mobile phase - A: water with 0.1% TFA, B: Acetonitrile with 0.1% TFA; gradient profile – From 0 to 25 min: 0–50% B; flow - 0.8 mL/min, oven temperature - 30°C.

even among peptides manufactured by the same synthetic route. The impurities can originate from raw materials, the manufacturing process, degradation or may be formed during storage. Although protecting groups, scavengers or activated functional groups are used to prevent undesired side-chain reactions the peptide manufacturing process leads to formation of closely related impurities. The most common impurities are products of racemization, deamidation, amino acid deletion or insertion, acetylation, oxidation, β-elimination, cyclization, reduction and incomplete deprotection [51]. The presence of related peptide impurities is typically determined using gradient reversed-phase HPLC method with UV detection, because of its selectivity, high sensitivity, low limit of detection, quantification and robustness. The developed HPLC method should allow sufficient separation of potential impurities from manufacturing process as well as degradation products. The acceptance criteria for related substances according to the Ph. Eur. General Monograph 2902 [4] are presented in **Table 2**.

Specific thresholds should be applied for impurities known to be unusually potent or to produce toxic or unacceptable pharmacological effects.

4.2.4 Metallic impurities

The presence of inorganic impurity should also be considered, in particular when radiolabeling of the peptide with radiometals is concerned. According to the Ph. Eur. general monograph (2902), the metal residues in peptides should be determined if the manufacturing process is known or suspected to lead to its presence, e.g. due to the use of specific metal catalyst (e.g. Pd) or metal containing reagents. The content for each of the following metals: Pt, Pd, Ir, Rh, Ru, Os, Mo, Ni, Cr, V, Pb, Hg, Cd, Tl in the peptide precursors are limited to 0.01%. The metal impurities are typically examined using atomic absorption spectrometry (AAS), inductively coupled plasma with atomic emission spectrometry detection (ICP-AES) or mass spectrometry detection (ICP-MS) techniques. Determination of residual metals in peptides can be crucial for precursors intended for radiometal labeling [55]. It has been proven that the presence of certain metals can significantly affect the labeling efficiency through competitive chelation.

4.2.5 Residual solvents

In addition to related substances the residual solvents are required to be examined as impurities in peptide precursors. Residual solvents in pharmaceuticals are defined as organic volatile chemicals that are used in the manufacturing process. The solvents are not completely removed by practical manufacturing techniques (e.g. lyophilization process). General guidelines established by the ICH divide solvents into three classes [56]. The Class 1 solvents should not be used in the final step of the manufacturing process of chemical precursors, because of toxicity and environmental impact. The use of the Class 2 solvents should be limited due to potential toxicity and Class 3 solvents are regarded as posing a lower risk to human

Reporting threshold	0.2 per cent
Identification threshold	2.0 per cent
Total unspecified impurities	Maximum 3.0 per cent

Table 2.
Acceptance criteria for related substances [4].

health. Based on the permitted daily exposure (PDE), Class 2 and 3 solvents are limited to 0.5%. Residual solvents are typically determined using chromatographic techniques such as gas chromatography (GC) coupled with static headspace sampling. Many solvents are usually used in the peptides synthetic process. However, as the advantage of the SPPS and lyophilization process, the most frequently detected solvent is only acetonitrile (Class 2 solvent), used as the component of the mobile phase in the final purification process by preparative HPLC.

4.2.6 Counter-ion content

Synthetic peptides usually contain counter-ions on protonated amino functional groups (N-terminus, Arg, His, Lys, etc.). The presence of counter-ions such as acetate, chloride or trifluoroacetate results from the peptide post synthetic cleavage and/or purification process. Depending on the peptide sequence they reduce the net peptide content by 5 to 25%, but are not considered as impurity. Radiopharmaceutical preparations for diagnostic or therapeutic purposes are based on the net peptide content and thus the amount of residual counter-ions needs to be assessed. To determine counter-ion amounts different method are being used such as: GC, HPLC-UV or ion chromatography (IC). Trifluoroacetic acid (TFA) determined by IC at the level of ca. 20% in DOTA-TATE [52], corresponded to three TFA molecules associated to single peptide molecule. TFA is commonly used as a chemical reagent to remove residual protecting groups during purification of peptides and also as a mobile-phase modifier in a reversed-phase chromatography. Therefore, when the counter-ion finally is AcOH or HCl, determination of the TFA residual content is mandatory.

4.2.7 Water content

In order demonstrate a lot-to-lot consistency the test for water content (residual moisture remaining from the lyophilization process) should be also performed. This parameter may affect the stability of the peptide. For residual water Karl-Fischer titration method as well as GC method with thermal conductivity detector (TCD) [57] are commonly used and water content is limited to max. 10%.

4.2.8 Assay

Generally, assay is defined as a net peptide content. The lyophilized peptide contains also water, counter ions and residual solvents. The net peptide content is referred to percentage of peptide material in the lyophilized peptide. According to ICH guideline Q6A, a specific stability-indicating procedure should be included in the specifications to determine the content of the drug substance. There are two main approaches to determine net peptide content. The first method is a relative assay against a well-defined chemical reference substance, performed using comparative chromatographic procedures. Usually the same RP-HPLC method is used for both assay, identification and related substances. The second approach is an absolute assays involving a functional group (e.g. AAA or titration methods) or a nitrogen content analysis. The nitrogen content is determined from the results of elemental analysis CHN. The calculation of the net peptide content is based on the relation between determined %N to the theoretical content in the peptide structure. For example, this method was used to DOTA-TATE assay determination. Peptide content calculated from elemental analysis was ca. 78.0%, which was in agreement with the generally accepted limit ≥75% [52].

4.2.9 Microbiological assays

The presence of microorganisms may affect the stability of drug substances due to their propensity to degrade/metabolize peptides. Microbiological examinations involve the bioburden control (Ph. Eur 2.6.12) and content of bacterial endotoxins (Ph Eur. 2.6.14). The microbial enumeration tests for total aerobic microbial counts (TAMC) and total yeast and mold counts (TYMC) must adhere to the acceptance criteria of 10^3 CFU/g and 10^2 CFU/g for bulk material and 10^2 CFU/g and 10^1 CFU per container for chemical precursors packed in single and multi-dose containers, respectively. Bacterial endotoxin can be determined by the gel-clot or photometric methods (turbidimetric and chromogenic techniques) and acceptance criteria are limited to a maximum 100 IU/g for bulk material or maximum 10 IU per container for chemical precursors packed in single-dose and multidose containers.

5. Radionuclide precursors

Radionuclide precursors are offered as solutions for radiolabeling with MA, they are also locally produced for the in-house preparation of radiopharmaceuticals. There is an ongoing debate whether radionuclide precursors always have to be considered as medicinal product, or also can be provided as a starting material [58]. Unlike for chemical precursors for radiopharmaceutical preparation, up to date there is no monograph in the Ph. Eur. that sets out general requirements for radionuclide precursors. This is due to the fact that the quality requirements for radionuclides used to obtain diagnostic and therapeutic preparations are highly varying and depend on the irradiation route and chemical processing involved, which mainly affect the parameters of radionuclide purity or specific activity.

However, there are several individual Ph. Eur. monographs for radionuclide precursors. Two of these concern radionuclide precursors used to prepare radiopharmaceuticals for therapeutic use. These are: *Lutetium (^{177}Lu) solution for radiolabelling* (mon. 2798) [59] and *Yttrium (^{90}Y) chloride solution for radiolabelling* (mon. 2803) [60]. There are also six monographs published for radionuclide precursors for preparation of diagnostic radiopharmaceuticals: Fluoride (^{18}F) solution for radiolabelling (mon. 2390) [61], Sodium iodide (^{123}I) solution for radiolabelling (mon. 2314) [62], Sodium iodide (^{131}I) solution for radiolabelling (mon. 2121) [63], Indium (^{111}In) chloride solution (mon. 1227) [64] and Gallium (^{68}Ga) chloride solution for radiolabelling (mon. 2464) [65] and a newly published monograph for Gallium (^{68}Ga) chloride (accelerator-produced) solution for radiolabelling (mon. 3109) [66].

Focusing attention on theranostic radiopharmaceuticals, herein the quality requirements only for metallic radionuclide precursors used in diagnostics and therapy are compared. **Table 3** shows the exemplary quality requirements for radionuclide precursor for therapeutic use (^{177}Lu) and a matching radionuclide precursor for diagnostic use (^{68}Ga).

Comparing the requirements of these two monographs there are apparently large differences in numerical values seen, especially for metal ion content and radiochemical purity. However, when the radioactivity of these radionuclides (different for therapeutic or diagnostic use) is considered, there are basically no differences in quality requirements for both radionuclides. This can be demonstrated on the example of the DOTA-TATE preparations with ^{177}Lu and ^{68}Ga. For therapy 7.4 GBq of [^{177}Lu]Lu-DOTA-TATE is used and this preparation contains ca. 0.2 mg of DOTA-TATE. Typical dose of [^{68}Ga]Ga-DOTA-TATE is 200 MBq and the ligand content in the preparation should not exceed 0.05 mg. Therefore, when analyzing the limit of metallic impurities, e.g. Zn in the radionuclide precursor,

Lutetium (^{177}Lu) solution for radiolabelling (Ph. Eur. 2798 [59])	**Gallium (^{68}Ga) chloride solution for radiolabelling (Ph. Eur. 2464 [60])**
pH: 1.0 to 2.0, using a pH indicator strip R.	*pH:* maximum 2, using a pH indicator strip R.
Lutetium: Inductively coupled plasma-atomic emission spectrometry (2.2.57), for determination of specific radioactivity. *Copper:* maximum 1.0 μg/GBq *Iron:* maximum 0.5 μg/GBq *Lead:* maximum 0.5 μg/GBq *Zinc:* maximum 1.0 μg/GBq	*Iron:* maximum 10 μg/GBq *Zinc:* maximum 10 μg/GBq
RADIONUCLIDIC PURITY *Lutetium-177*: minimum 99.9 per cent of the total radioactivity. Gamma-ray spectrometry. *Results*: - the total radioactivity due to ytterbium-175 (impurity B) is not more than 0.1 per cent; – the total radioactivity due to lutetium-177 m (impurity A) is not more than 0.07 per cent; – the total radioactivity due to radionuclidic impurities other than A and B is not more than 0.01 per cent.	RADIONUCLIDIC PURITY *Gallium-68:* minimum 99.9 per cent of the total radioactivity. A. Gamma-ray spectrometry. *Limit*: peaks in the gamma-ray spectrum corresponding to photons with an energy different from 0.511 MeV, 1.077 MeV, 1.022 MeV and 1.883 MeV represent not more than 0.1 per cent of the total radioactivity. B. Germanium-68 and gamma-ray-emitting impurities. Gamma-ray spectrometry. *Result*: the total radioactivity due to germanium-68 and gamma-ray-emitting impurities is not more than 0.001 per cent.
RADIOCHEMICAL PURITY *[^{177}Lu]lutetium(III) ion*: minimum 99 per cent of the total radioactivity due to lutetium-177.	RADIOCHEMICAL PURITY *[^{68}Ga]gallium(III) ion*: minimum 95 per cent of the total radioactivity due to gallium-68.
Bacterial endotoxins (2.6.14): less than 175 IU/V, V being the maximum volume to be used for the preparation of a single patient dose, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.	*Bacterial endotoxins (2.6.14):* less than 175 IU/V, V being the maximum volume to be used for the preparation of a single patient dose, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.
Sterility: If intended for use in the manufacture of parenteral preparations without a further appropriate sterilization procedure, it complies with the test for sterility prescribed in the mon. 0125. The preparation may be released for use before completion of the test.	

Table 3.
Comparison of Ph. Eur. requirements for selected radionuclide precursors.

similar values are obtained in both cases, i.e. maximum 37 ng and 40 ng per microgram of DOTA-TATE for lutetium-177 and gallium-68, respectively.

When the radiochemical purity is compared, the higher limit of permissible other forms of diagnostic radionuclide ([^{68}Ga]gallium(III) ion: minimum 95%) than for the therapeutic radionuclide ([^{177}Lu]Lutetium(III) ion: minimum 99%) does not result in a higher risk to the patient. Thus, 5% of other forms of a trivalent gallium-68 ion may result in the deposit of 10 MBq of this radionuclide in undesirable chemical form in non-target organs, while for 1% lutetium-177 it is as much as 74 MBq of uncontrolled chemical form. However, it must be noted that a stricter limit for the latter radionuclide is difficult to achieve due to the limitations of the analytical methods, which are characterized by an approximate 1% uncertainty of determination.

Bearing in mind that the differences in the profile of radionuclide contamination depend on the radionuclide production process [67], it is unlikely that uniform quality requirements for radionuclide precursors will be set in numerical terms. Each radionuclide precursor should be evaluated on a case-by-case basis, taking into account the physical characteristics of the radionuclide, its mode of irradiation and chemical processing as well as the envisaged clinical use and the dose planned for administration to the patient. This is clearly reflected in monographs referred in this Chapter. The monograph for ^{177}Lu [59] applies to both the direct and indirect production routes of ^{177}Lu in nuclear reactors and covers all quality aspects regardless the different specific radioactivity and impurity profiles. The decision is left to the producer of the final radiopharmaceutical preparation to use the appropriate solution for radiolabeling. However, the relevant information needs to be stated on the label. This is different in case of ^{68}Ga, there are two different monographs specifying its quality requirements depending whether it's generator [65] or accelerator produced [66]. One can expect that a similar individual approach applies to the future monographs for new theranostic radionuclides, for example ^{47}Sc, which can be either accelerator or reactor produced [68].

6. Conclusion

Are the requirements for radiopharmaceutical precursors overregulated? With the development of new theranostic procedures involving radiopharmaceuticals, there is a need for proper qualitative evaluation of the final radiopharmaceutical preparation and both of the radiopharmaceutical precursors to ensure efficacy and safety of the treatment. An excellent example of the long pathway of a radiopharmaceutical, ^{111}In-CP04, a peptide targeting the cholecystokinin-2 receptor, from the preclinical development over establishing the required pharmaceutical documentation to designing and submitting a clinical trial in patients with Medullary Thyroid Carcinoma, was recently presented [16]. All the quality aspects of CP04 as chemical precursor have been addressed in the IMPD in view of the quality and suitability of the radiolabeled preparation, ^{111}In-CP04, in order to bring it to the clinic.

In this Chapter, the quality requirements applicable to radiopharmaceutical precursors in the context of their regulatory status in Europe were reviewed. EMA and Ph. Eur. provide public standards for manufacture and quality control of these precursors by establishing specifications and acceptance criteria. While in the case of radiopharmaceuticals with MA and CT regulations quite strictly define the quality and documentation requirements, such standards for in-house produced radiopharmaceuticals are still awaited.

DOI: http://dx.doi.org/10.5772/intechopen.95438

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