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An Overview of PET Radiopharmaceuticals in Clinical Use: Regulatory, Quality and Pharmacopeia Monographs of the United States and Europe

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Abstract

Since 1976, more and more PET radiopharmaceuticals have been developed as the clinical introduction of [^{18}F]FDG for various medical applications. However, few of them could be involved in routinely clinical use in hospitals partly because of restrictions in regulatory and facilities. This chapter aims to provide an overview of PET radiopharmaceuticals that are common manufactured (or prepared) in industry (or hospitals) about regulatory and quality aspects, and further summarize pharmacopeia-listed PET radiopharmaceuticals and their clinical usefulness herein. Particularly, PET radiopharmaceuticals listed in latest United States Pharmacopeia (USP) and/or European Pharmacopeia (EP) are included for this chapter. Finally, this chapter would be helpful in the basic understanding of clinical PET radiopharmaceuticals for physicians or technologists.

Keywords: PET, radiopharmaceutical, regulation, quality, clinical application, USP, EP, pharmacopeia

1. Introduction

Positron emission tomography (PET) radiopharmaceutical is composed of a biologically active pharmacophore and a positron-emitting radionuclide, and belongs to a unique species in pharmaceutical field. The most common radionuclides for PET radiopharmaceuticals include ^{11}C , ^{15}O , ^{13}N , ^{18}F , ^{68}Ga and ^{82}Rb (**Table 1**). In addition to radiation issue, short half-lives of these positron emitters (78 sec~110 min) definitely result in unavoidable limitations on manufacturing (including production and following quality control (QC) analyses) and clinical use of PET radiopharmaceuticals. Above are all practical challenges for a conventional

Radionuclide	Half-life	Max specific activity (Ci/ μ mol)	β^+ (%)	Max E_β (MeV)	Max β^+ range (mm)	Production route
^{11}C	20 min	9220	99	0.96	4.1	Cyclotron
^{15}O	123 sec	90,800	100	1.19	5.1	Cyclotron
^{13}N	10 min	18,900	100	1.72	7.3	Cyclotron
^{18}F	110 min	1710	97	0.635	2.4	Cyclotron
^{68}Ga	68 min	2766	88	1.9	8.2	Cyclotron/ Generator
^{82}Rb	78 sec	150,400	95	3.35	14.1	Generator

Table 1. Characteristics of common positron emitters.

pharmaceutical industry. Hence, commercial large-scale manufacturing and small-scale preparation of PET radiopharmaceuticals are respectively allowed in radiopharmaceutical industries and the radiopharmacy of hospitals in most countries worldwide. Moreover, both practices in radiopharmaceutical industries and hospitals are clearly regulated by national competence authorities, such as Food and Drug Administration (FDA) of the United States (U.S.) and *European Medicines Agency* (EMA) of the European Union (EU).

In the other hand, a pharmacopeia is a national compendium of drug quality standards, such as U.S. Pharmacopeia (USP) and European Pharmacopeia (EP), and is always recognized as an official compendium. Drug standards listed in pharmacopeia monographs are usually enforced to be compliance under drug-related provisions at national level in order to prevent the marketing of inconsistent drugs and to reduce possible risks in public health. Although PET radiopharmaceuticals listing in pharmacopeia monographs sometimes do not mean for marketing authorization under national approval and reimbursement decision of medical insurance [1], some countries have enabled the clinical use (i.e., use for routine patient care with/without reimbursement or with/without national approval) or clinical trials as long as their qualities are in conformity with USP or EP standards, even no good manufacturing practice (GMP)-compliant process. Moreover, for those clinical studies using national-approved PET radiopharmaceutical for off-label indications, burdensome submission of an investigational new drug (IND) application will not be required in some countries.

In the other hand, specific QC procedures and specification of some PET radiopharmaceuticals have been listed in USP or EP. However, because of short half-lives of PET radiopharmaceuticals, QC tests prior to human administration within such a short period is a huge challenge. As a result, some quality exceptions are usually allowed for PET radiopharmaceuticals. Also, several efficient and quick tests have been developed for rapid QC tests of clinical PET radiopharmaceuticals.

This chapter first aims to provide an overview of regulations of manufacturing and clinical use of PET radiopharmaceuticals in U.S. and Europe. Secondly, the chapter will introduce the general quality aspect for PET radiopharmaceuticals. Finally, this chapter will end with the brief introduction of PET radiopharmaceuticals listed in the monographs of latest USP (USP 40) or EP (EP 9.0) (**Table 2**).

Radionuclide	Compound	USP	EP
¹¹ C	[¹¹ C]CO	✓*	
	[¹¹ C-methyl]Methionine	✓*	✓
	N-[¹¹ C-methyl]Flumazenil	✓*	✓
	[¹¹ C]N-methylspiroperidol	✓*	
	[¹¹ C-methoxy]Raclopride	✓*	✓
	[1- ¹¹ C]Sodium Acetate	✓*	✓
¹³ N	[¹³ N]NH ₃	✓	✓
¹⁵ O	[¹⁵ O]CO		✓
	[¹⁵ O]H ₂ O	✓*	✓
¹⁸ F	[¹⁸ F]FCH		✓
	[¹⁸ F]FDG	✓	✓
	[¹⁸ F]FDOPA (prepared by electrophilic substitution)	✓*	✓
	[¹⁸ F]FET		✓
	[¹⁸ F]FLT		✓
	[¹⁸ F]FMISO		✓
	[¹⁸ F]NaF	✓	✓
	[⁶⁸ Ga]Ga-Citrate		✓
⁶⁸ Ga	[⁶⁸ Ga]Ga-DOTA-TOC		✓
⁸² Rb	[⁸² Rb]rubidium chloride	✓	

*These monographs of 8 FDA-unapproved PET radiopharmaceuticals have been omitted from USP since May 1, 2015 (USP 38).

Table 2. PET radiopharmaceuticals listed in USP and EP.

2. Regulatory aspects of PET radiopharmaceuticals in the USA and Europe

2.1. USA regulatory view

In U.S., the clinical use of all radiopharmaceuticals has been regulated by FDA since 1975. Briefly, the regulatory process can be divided into two types. They are: 1. IND submission for investigational and research purposes by an individual or a commercial manufacturer, and 2. submissions of Notice of Claimed Investigational Exemption (NCIE), an abbreviated new drug application (ANDA) or New Drug Application (NDA) for commercial marketing only by a commercial manufacturer. However, because of the increasing clinical need of PET radiopharmaceuticals, based on FDA Modernization Act (FDAMA) in 1997 [2], PET radiopharmaceuticals were first categorized as positron-emitting drugs. In the same time, all PET radiopharmaceutical manufacturing facilities in U.S. were programmatically to compliant with PET drug GMP-compliance guideline or with USP General Chapter <823> [3], and further registered as manufacturers. Till now, these legal manufacturers could on-site (*in-house*) produced PET radiopharmaceuticals with same specifications listed in USP monographs.

In the other hand, USP is annually published by a nonprofit organization since 1820, U.S. Pharmacopeial Convention, and such organization also worked with FDA and specialists in academia and companies to establish monographs or general chapters. Typically, USP monographs are typically developed after FDA approval of the drug product for commercial marketing and thus a USP monograph of an FDA-approved drug has been used as one basis for a reimbursement decision. The first USP monograph for a PET drug was published in 1990 [4] and it described the quality specification and analytic methods for [^{18}F]FDG injection. However, there had been an exception for 4 approved and 8 unapproved PET drugs listed in USP monographs till 2013. Moreover, not only these 12 monographs were provided to U.S. Pharmacopeial Convention by various academic sponsors with un-validated data and outdated analytic methods, but also these unapproved 8 PET drugs have limited commercial application without FDA-approved NDA or ANDA. Consequently, based on recommendations of the Society of Nuclear Medicine and Molecular Imaging (SNMMI) Committee [1], U.S. Pharmacopeial Convention announced the omission of the monographs of 8 unapproved PET drugs on June 2014 and the omission initiative became official on December 1, 2014.

2.2. European regulatory view

In Europe, radiopharmaceuticals have been recognized as a special group of medicines. Thus, the preparation and clinical use of PET radiopharmaceuticals have been regulated and variously adopted by member states. Similar to USP, EP has legal status in Europe. Compared to the USA, EP is only for drug quality and is independent of licensing status or clinical utility of such drug. Regarding to PET radiopharmaceuticals, corresponding monographs are elaborated by a group that is composed of academic, commercial and regulatory specialists. From another point of view, a number of EU member states have set up a regulatory framework from the definitions of “magistral and officinal formulae” that is listed in Article 3 of Directive 2001/83 [5]. Additionally, “in-house” small-scale preparation of PET radiopharmaceuticals is allowed without the requirements of a marketing authorization based on various national laws of European countries [5]. Both a general chapter of EP entitled “Extemporaneous Preparation of Radiopharmaceuticals” [6] and the new PIC/S guidance document with Annex 3 on radiopharmaceuticals [7] are published and worked as comprehensive guidelines for such magistral approach. Furthermore, because of the special characteristics of PET radiopharmaceuticals, the clinical studies using diagnostic radiopharmaceuticals do not fall within the GMP-compliance regulations of conventional drugs from EU Regulation no 536/2014 of 16 April 2014 [8, 9]. On brief summary, no matter EP or PIC/S document, they both clearly define a clear distinction between PET radiopharmaceuticals and conventional medicine, and further provide the corresponding guidance. All would be significantly helpful and powerful in promotion and development of PET radiopharmaceuticals in Europe.

3. Quality aspects of PET radiopharmaceuticals

Even costly implementation and maintenance of quality system for a PET radiopharmaceutical manufacturing (or preparing) site [10, 11], it is still thought to be cost-effective [12]. Moreover, it will be helpful for qualified patient care, regulatory requirements, optimization

of safety and efficacy for patient care and a reliable quantitative performance in both diagnostic and therapeutic nuclear medicine procedures [13]. Therefore, GMP-compliant PET manufacturing (or preparing) process including production, QC, quality assurance (QA), package and distribution has been required by competent authorities in many countries worldwide. Furthermore, during these years, the concept of “Quality by Design (QbD)” based on guidelines of International Conference on Harmonization (ICH) (ICH Q8 [14], ICH Q9 [15], and ICH Q10 [16]) has been the fundamental topic in pharmaceutical field and an appropriate quality system has been widely required to implement in many radiopharmaceutical manufacturing sites (**Figure 1**). Briefly, QA covers whole process and GMP specifically characterizes those production and QC activities that guarantee products are produced under the constant scrutiny of quality standards [17], although the association of QA, GMP, and QC throughout whole pharmaceutical process is slightly different in various guidelines.

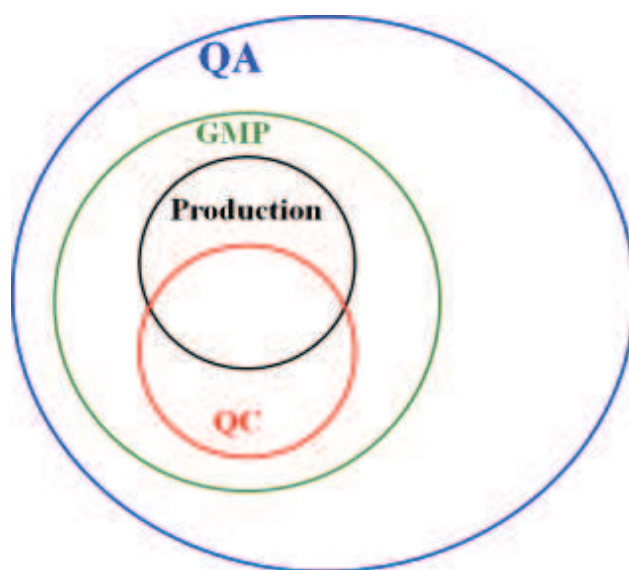


Figure 1. The inter-relationship for whole quality system in PET radiopharmaceutical manufacturing.

Particularly, QC procedure of PET radiopharmaceutical is usually critical and essential, since it is synthesized every day or is small-scale “prepared” in radiopharmacy of a hospital. A typical QC programme of a PET radiopharmaceutical is involved from radionuclide production to final product release and a series of QC tests for PET radiopharmaceuticals basically include:

1. Appearance, by visual assessment;
2. pH determination;
3. Radionuclidic identification, by gamma-ray spectrometry or half-life measurement;
4. Radionuclidic purity, by gamma-ray spectrometry;
5. Chemical purity, by high-pressure liquid chromatography (HPLC) or by thin-layer chromatography (TLC);
6. Radiochemical purity, by HPLC with a radioactivity detector or by TLC with a radioactivity scanner;

7. Residual solvents, by gas chromatography (GC);
8. Bacterial endotoxins, by a rabbit test or limulus amebocyte lysate (LAL) test;
9. Radioactivity, by a validated dose calibrator and.
10. Sterility, by incubating the sample with fluid thioglycollate medium (FTM) at 30~35°C for 14 days or with soybean casein digest (SCD) medium at 20~25°C for 14 days.

However, because of short-lives of PET radiopharmaceuticals, some lengthy tests cannot be performed prior to release for human use and are allowable to perform within a short time after the release. Furthermore, in addition to the limited time for QC of PET radiopharmaceuticals, limited personnel for *in-house* preparing of PET radiopharmaceuticals is another major issue for a hospital. Therefore, more and more efficient systems have been developed and successfully implemented for clinical use, such as Endosafe® Portable Testing System™ (PTS™) for rapid endotoxin testing (Charles River, Wilmington, MA) (<https://www.criver.com/products-services/qc-microbial-solutions/endotoxin-testing/endotoxin-testing-systems/endosafe-nexgen-pts?region=3681>) and Tracer-QC system for automation of QC tests of PET radiopharmaceuticals (LabLogic Systems Ltd., Sheffield, UK) (<https://lablogic.com/nuclear-medicine-and-pet/instruments/tracer-qc>).

4. Overview of current PET radiopharmaceuticals listed in USP or EP

4.1. [¹¹C-methyl]Methionine injection (EP)

Cellular protein synthesis is a well-control process for enzymes, membrane receptors, structural proteins, and growth factors [18]. Most importantly, increased cellular protein synthesis is often characterized in malignant growth [19]. Otherwise, decreased protein synthesis is found in certain neurodegenerative disorders [20]. Thus, the ability to *in vivo* visualize the protein synthesis rate is critical for clinic. Protein synthesis is initiated universally with the amino acid, methionine [21]. Therefore, one of ¹¹C-labeled methionine analogs, [¹¹C-methyl]methionine ([¹¹C]MET) [22] (**Figure 2**), has been used for imaging of rate of protein synthesis [23, 24], although the short physical half-life of ¹¹C (20 min) limits its accessibility for PET scanning centers without a cyclotron. Clinically, [¹¹C]MET has been used in imaging of brain, urinary, gynecological, liver and lung cancer [25–28]. Particularly, the enhanced transport of [¹¹C]MET into the brain has been known via the reversible sodium-independent transport system L (LAT 1) since 1995 [28] and increased LAT1 expression has been found in glioma and many other cancers and is associated with high grade and poor prognosis [29–32], thus [¹¹C]MET has been widely in various brain tumors [33, 34].

4.2. N-[¹¹C-methyl]Flumazenil injection (EP)

The GABA_A/benzodiazepine receptor complex is also known as the central benzodiazepine receptor and specifically mediates all pharmacologic properties of ethanol, zinc, picrotoxin and some drugs such as benzodiazepines (sedative, anxiolytic, anticonvulsant, myorelaxant),

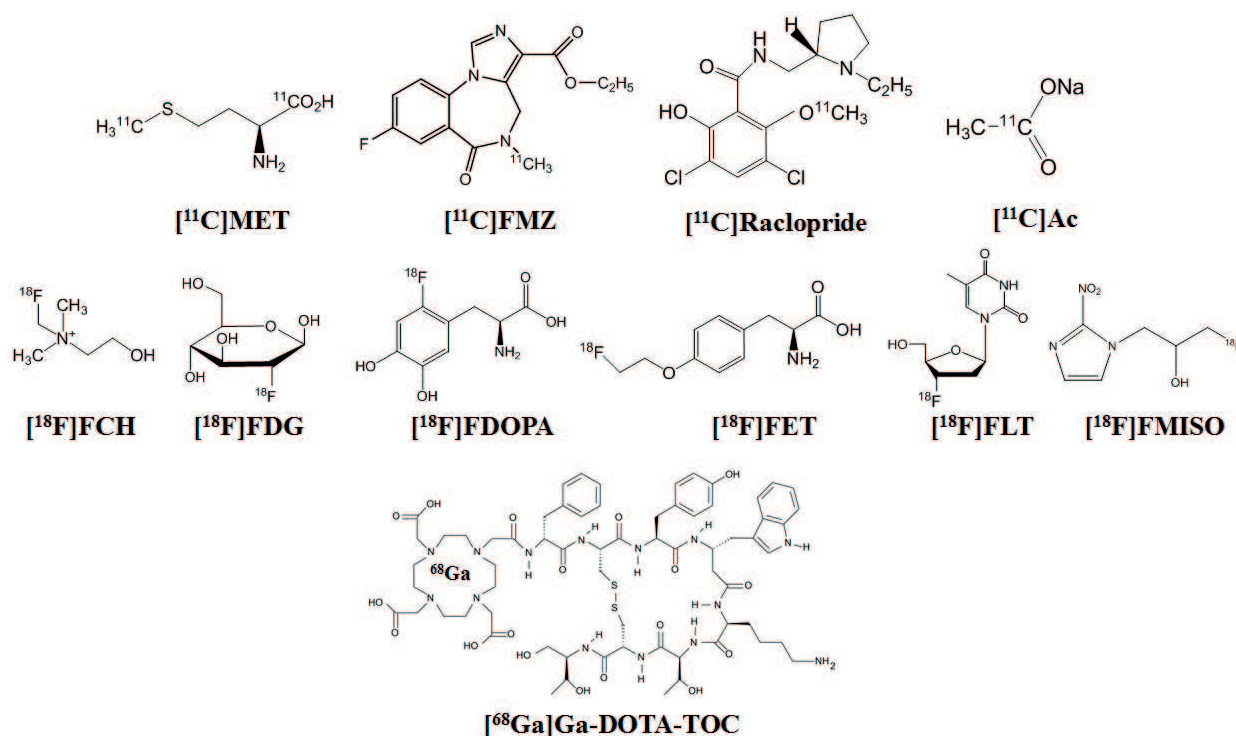


Figure 2. Chemical structures of PET radiopharmaceuticals listed in this chapter.

barbiturates (cerebral protection) and neuroactive steroids [35]. Based on a benzodiazepine antagonist, N-[¹¹C-methyl]Flumazenil (**[¹¹C]FMZ**) (**Figure 2**) [36] has been developed and known for its excellent kinetic properties for the image quantification [37]. Moreover, [¹¹C]FMZ has been considered as a versatile PET tracer for assessment of several conditions, such as neuronal damage in head injury [38], epilepsy [39], stroke-induced penumbral areas of infarction [40] and Alzheimer's disease (AD) [41].

4.3. [¹¹C-methoxy]Raclopride injection (EP)

Dopamine (DA) plays an important role in every-day brain functions including experiencing pleasure, regulating attention, and learning to control urges. Dysfunction of DA circuits has been thought to be related to various psychiatric diseases such as Parkinson's diseases (PD), addiction, attention-deficit hyperactivity disorder, and schizophrenia [42]. Studying *in vivo* dopamine function in humans became possible in the mid-1990s with the development of [¹¹C]raclopride (**Figure 2**) [43, 44], which originates from a DA receptor antagonist (D₂/D₃) with moderate affinity and reversible binding characteristics. Up to now, [¹¹C]raclopride is the most widely used PET radiopharmaceutical for measuring DA changes in striatal dopamine levels in the synapse before and after pharmacological and behavioral challenges [45], such as aging [46–48], schizophrenia [49–53] and PD [54, 55].

4.4. [1-¹¹C]sodium acetate injection (EP)

Acetate is a molecule quickly picked-up by cells to convert into acetyl-CoA by acetyl-CoA synthetase (EC 6.2.1.1 according to Enzyme Commission Number) and participates in

cytoplasmic lipid synthesis, which is believed to be increased in tumors. Thus, $[1\text{-}^{11}\text{C}]$ Sodium Acetate ($[^{11}\text{C}]\text{Ac}$) (**Figure 2**) [56, 57] has been proved clinical usefulness in prostate cancer (PC) [58], hepatocellular carcinoma (HCC), lung cancer, nasopharyngeal carcinoma [33], renal cell carcinoma, bladder carcinoma and brain tumors [59]. Furthermore, $[^{11}\text{C}]\text{Ac}$ has been used to clinically measure myocardial oxygen consumption since 2010 [60] and used in some rare conditions, such as thymoma, cerebellopontine angle schwannoma, angiomyolipoma of the kidney, encephalitis, and multiple myeloma [59].

4.5. $[^{13}\text{N}]\text{NH}_3$ injection (USP and EP)

Coronary flow reserve (CFR) is calculated as the ratio of hyperemic to rest absolute myocardial blood flow (MBF) and is a particularly useful parameter in the assessment of adverse cardiovascular events such as epicardial coronary stenosis, diffuse atherosclerosis, and microvascular dysfunction on myocardial tissue perfusion [61]. Routinely used $[^{13}\text{N}]\text{Ammonia}$ ($[^{13}\text{N}]\text{NH}_3$) is not only a useful ^{13}N -labeled PET imaging agent for assessing regional blood flow in tissues [62], but a well-validated radiotracer for clinical management of patients with coronary artery disease [62–64]. Moreover, recently $[^{13}\text{N}]\text{NH}_3$ has been used in PC, because the up-regulation of NH_3 during *de novo* glutamine synthesis was known in tumors [65]. Furthermore, because excess circulating NH_3 is neurotoxic and hyperammonemia is thought to be a major factor in the encephalopathy associated with several diseases, such as liver cirrhosis [66–68], $[^{13}\text{N}]\text{NH}_3$ is also used for elucidation of NH_3 metabolism in patients with hepatic encephalopathy [69].

4.6. $[^{15}\text{O}]\text{CO}$ injection (EP)

$[^{15}\text{O}]\text{CO}$ is one of the most common tracers used for noninvasively measuring oxygen consumption and blood volume [70, 71]. Additionally, $[^{15}\text{O}]\text{CO}$ is crucial for the evaluation of acute stroke patients. Moreover, measurement of myocardial oxygen consumption is a useful tool to clarify the relationship between MBF and oxygen extraction fraction (OEF), because both OEF and MBF are important indicators in describing myocardial function [72].

4.7. $[^{15}\text{O}]\text{H}_2\text{O}$ injection (EP)

Although the short half-life (123 sec) of ^{15}O results in the challenges in clinical use, $[^{15}\text{O}]\text{H}_2\text{O}$ is still the preferred tracer because of its ease production from generator, effectiveness and safety for patient use [73]. Particularly, PET with $[^{15}\text{O}]\text{H}_2\text{O}$ has been a standard method and most reliable approach for quantitative measurement of cerebral blood flow (CBF). Also, $[^{15}\text{O}]\text{H}_2\text{O}$ is capable to clinically investigate cerebral and myocardial perfusion [74], and tumor perfusion [75, 76].

4.8. $[^{18}\text{F}]\text{FCH}$ injection (EP)

Choline is a precursor for the biosynthesis of phospholipids which are essential components of all membranes and is phosphorylated by choline kinase (CK) to produce phosphatidylcholine. Upregulated CK is known in cancer cells, thus it further leads to increased uptake of choline in tumor cells with the excess need for phospholipid biosynthesis [77, 78]. Consequently, ^{18}F -labeled choline analogs, $[^{18}\text{F}]\text{fluoromethylcholine}$ ($[^{18}\text{F}]\text{FCH}$) (**Figure 2**) [79, 80] has been a promising tumor imaging agents for various types of tumors include brain [80], breast,

thyroid, lung, liver and prostate [81]. Particularly, [¹⁸F]FCH has been shown to be better than [¹⁸F]FDG for PC and HCC detections [81].

4.9. [¹⁸F]FDG injection (USP and EP)

Since its synthesis in 1976, 2-fluorine-[¹⁸F]fluorodeoxyglucose ([¹⁸F]FDG) [82] (**Figure 2**) has been the most widely used radiotracer for PET studies in neuroscience, cardiology and oncology (**Table 3**) [83]. After FDA approval in 1997, [¹⁸F]FDG with PET or PET/CT scanner became an established imaging tool in the clinical assessment of many neoplasms, as well as the nonmalignant diseases including dementia, myocardial ischaemia, inflammation and infection [84].

4.10. [¹⁸F]FDOPA (prepared by electrophilic substitution) injection (EP)

Dihydroxyphenylalanine (DOPA) has been known as an intermediate in the catecholamine synthesis pathway. One of the ¹⁸F-radiolabeled analogs, 3,4-dihydroxy-6-[¹⁸F]fluoro-L-phenylalanine ([¹⁸F]FDOPA) (**Figure 2**), was first reported as a PET tracer for imaging pre-synaptic dopaminergic functions in 1983 [85]. Subsequent studies revealed the utility of [¹⁸F]FDOPA for the visualization of various peripheral tumor entities via PET [86], which can be attributed to the up-regulation of amino acid transporters in malignant tissues due to an often increased proliferation [87]. In particular, because of the relationship between the expression of aromatic L-amino acid decarboxylase (AADC) and the metabolism of [¹⁸F]FDOPA [88, 89], [¹⁸F]FDOPA has shown diagnostic advantages in the imaging of neuroendocrine cell-related malignancies like neuroendocrine tumors (NETs) [89–94], pheochromocytoma [95–97], pancreatic adenocarcinoma [98, 99] and neuroblastoma (NB) [100–102] regarding diagnostic efficiency and sensitivity.

Classification	Disease	Application
Neurology	Alzheimer’s Disease	—
	Epilepsy	Pre-surgical evaluation for epileptogenic foci (85–90% accuracy).
Cardiology	Myocardial Viability	Assessment of myocardial viability prior to cardiac surgery
	Identify high-risk patients	Select patients who will benefit from bypass
Psychiatry	Schizophrenia	—
	Depression	—
Oncology	Tumor Evaluation	Differentiate recurrent/residual tumor from necrosis.
	Tumor Staging	Malignant vs. benign. Lung nodules, primary breast and colon cancers.
	Tumor Monitoring	Response to therapy.
	Tumor Localization	Metastases, abnormal sites
Infection and Inflammation	Orthopedic infections	—

Table 3. Summary for clinical application of [¹⁸F]FDG [83].

4.11. [^{18}F]FET injection (EP)

Na^+ -independent system L amino acid transporters (LATs) preferentially transports amino acids with large neutral side chains, including L-leucine, L-phenylalanine, and L-tyrosine. O-(2- ^{18}F fluoroethyl)-L-tyrosine (^{18}F]FET) (**Figure 2**) [103] belongs to the class of large neutral amino acids, which are transported via specific amino acid transporters especially of LATs [104]. Although data today still not reveal which the transporter(s) responsible for ^{18}F]FET accumulation in cells [105], ^{18}F]FET has been well known for its high uptake in brain tumors and its potential for grading tumors particularly gliomas [106, 107]. Summarily, ^{18}F]FET has been well-investigated in differential diagnosis, grading, prognostication, treatment response assessment, and differentiating pseudoprogression from non-specific post-therapeutic changes [108–110]. Switzerland was the first country to approve ^{18}F]FET PET for clinical use in brain tumor imaging since 2014 [105].

4.12. [^{18}F]FLT (^{18}F]Alovudine) injection (EP)

Cellular proliferation plays an important role in cancer and has been an important imaging target of PET radiopharmaceuticals, especially with the aim targeting of DNA synthesis. Since the approach to the measurement of DNA synthesis in humans was explored in the early 1970s, based on an antiviral agent developed by Medivir, ^{18}F]fluorothymidine (^{18}F]FLT, also known as ^{18}F]Alovudine) (**Figure 2**) [111, 112] has been designed with intracellularly trapping of its phosphorylated metabolite within cells [113]. Up to now, ^{18}F]FLT has been widely investigated in oncologic setting comprising tumor detection, staging, restaging, and response assessment to treatment [114–116] and ^{18}F]FLT imaging has several clinical advantages including noninvasive procedure, three-dimensional tumor images and simultaneous detection of multiple tumor sites [117]. Also, ^{18}F]FLT is capable to evaluate tumor heterogeneity in day-to-day practice [118].

4.13. [^{18}F]FMISO injection (EP)

Hypoxia means insufficient oxygen availability of a cell occurring both in health and is acknowledged by the observation of Gray *et al.* in the mid-1950s [119, 120]. Hypoxia is an important prognostic indicator of response to either chemotherapy or radiation therapy in cancer management [121, 122]. Hypoxia is also an independent factor for predicting the metastases tendency of a tumor cell, because of its enhancement in DNA mutations of atypical cells and further appearance of more aggressive cells. Consequently, 1-(2-hydroxy-3- ^{18}F]fluoropropyl)-2-nitroimidazole (^{18}F]FMISO) (**Figure 2**) [123, 124] is the most established agent for assessing hypoxia and has been used for cancer imaging over the past 30 y for glioblastoma multiforme, non-small-cell lung cancer, and head and neck tumors [125]. In addition, high accuracy of ^{18}F]FMISO PET imaging for determining the duration of survival without relapses and for predicting the radiotherapy efficiency in patients with malignant tumors of various localizations has been reported [126, 127]. Furthermore, prognostic potential of ^{18}F]FMISO for the pretherapeutic tumor oxygenation status has been confirmed for glioblastoma multiforme, head and neck cancer, lung cancer, breast cancer, pancreatic cancer, gynecologic cancers, cervical cancer and sarcoma [127].

4.14. [^{18}F]NaF injection (USP and EP)

The bone is the most common place of tumor metastases next to the lung and liver [128]. Therefore, early and accurate diagnosis of the metastatic bone diseases thus plays an important

role for an establishment of adequate therapeutic strategy [129]. [^{18}F]Sodium fluoride (^{18}F]NaF) was introduced in 1962 and approved by FDA in 1972 [130]. [^{18}F]NaF is a high sensitive bone-seeking PET radiopharmaceutical and is considered as an excellent substitute for traditionally used $^{99\text{m}}\text{Tc}$ -labeled tracers, because its favorable characteristics of negligible protein binding, and rapid blood pool clearance. With $^{99\text{m}}\text{Tc}$ supply around the world is gradually become a crisis due to the shortage of ^{99}Mo -source material [131, 132], the clinical use of [^{18}F]NaF keeps increasing worldwide. Additionally, uptake of [^{18}F]NaF reflects blood flow and bone remodeling [133], and [^{18}F]NaF have been proposed for the use in detection of benign and malignant osseous abnormalities that also allows the regional characterization of lesions in metabolic bone diseases [134, 135].

4.15. [^{68}Ga]Ga-citrate injection(EP)

In addition to war and famine, bacterial infection has still been one of major worldwide causes for human morbidity and mortality for centuries [136, 137]. Because of the trapping of gallium in the extravascular compartment for inflammatory or infectious sites with the increased capillary permeability [138], and the iron-like binding characteristics in bacterial siderophores and activated lactoferrin in neutrophils [139, 140], gallium is thought to be indirectly uptaken by macrophages [141, 142] or directly uptaken by bacteria [143]. Thus, [^{67}Ga]gallium citrate (^{68}Ga]Ga-Citrate) has been used for clinical imaging of infection and inflammation since 1984 [144]. The utilities of [^{68}Ga]Ga-Citrate include the monitoring of osteomyelitis, diskitis, intra-abdominal infection, tuberculosis and interstitial nephritis, as well as the localization of infection in patients with cellulitis and abscesses [145, 146].

4.16. [^{68}Ga]Ga-DOTA-TOC injection (EP)

NETs arised from neuroendocrine cells and are one of slow-growing tumors with year-by-year increased incidence rate and 75% of overall 5-y survival, which is strongly dependent on stage and grade of the tumor [147]. Because NETs has been known for its unique over-expression of somatostatin receptors (SSTrs) on the tumor cells [148], SSTr-targeting PET radiopharmaceuticals provide a promising and useful approach for both diagnostic imaging and further peptide receptor radionuclide therapy (PRRT), such as ^{68}Ga -labeled DOTA-(Tyr³)-octreotide acetate (^{68}Ga]Ga-DOTA-TOC) (**Figure 2**) [149]. Because octreotide is a subset of the amino acid in somatostatin and has been demonstrated to avidly bind to SSTr [150], [^{68}Ga]Ga-DOTA-TOC has been recognized for its affinity toward both the type 2 somatostatin receptor (SSTr2) and the type 5 somatostatin receptor (SSTr5) [151–154]. Also, [^{68}Ga]Ga-DOTA-TOC was the first PET radiopharmaceutical to clinically localize to NETs in 2001 [155] and has been widely used in Europe and several other countries to assist the therapy planning and accurate diagnosis of NETs patients [156]. In addition, [^{68}Ga]Ga-DOTA-TOC is valuable for neuroectodermal tumors, Hurthle cell thyroid carcinoma, prostate cancer patients with bone metastases and autoimmune thyroid disease like Graves' disease and Hashimoto's disease [145, 146].

4.17. [^{82}Rb]rubidium chloride (USP)

Just like previous described [^{13}N]NH₃ and [^{15}O]H₂O, [^{82}Rb]Rubidium chloride (^{82}Rb]RbCl) has been reported for directly proportional relationship between its uptake and MBF since 1954 [157]. In addition, several studies have demonstrated the good diagnostic accuracy of [^{82}Rb]RbCl

in monitoring of cardiac flow [158, 159]. Subsequently, $^{82}\text{Sr}/^{82}\text{Rb}$ generator (CardioGen-82®) of Bracco Diagnostics has been approved by FDA for clinical cardiac imaging since 1989 (NDA 19-414). Therefore, production and administration of ^{82}Rb]RbCl can be well coordinated with the $^{82}\text{Sr}/^{82}\text{Rb}$ generator in clinic [160], although a short half-life (78 sec) of ^{82}Rb . In brief, the clinical advantages of ^{82}Rb]RbCl cardiac imaging include its capacity to accurately quantify MBF and a low delivered radiation exposure for a rest/stress test resulted from its very short half-life [160].

5. Conclusion

With the development of imaging technology, more and more pharmaceutical industry and hospitals worldwide have paid attentions on clinical potential of PET radiopharmaceuticals. However, because of special characteristics of PET radiopharmaceuticals, current pharmaceutical regulatory is probably inapplicable and would be a hurdle for clinical use of PET radiopharmaceuticals in most countries. Thus, as these official monographs of PET radiopharmaceuticals listing in USP or EP, it is definitely worthy to work together for more pharmacopeia monographs and a PET radiopharmaceutical-specific regulatory for benefits of patient-centered care in the future.

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Conflict of interest

We declare no conflict of interest.

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