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PHARMACOPOEIAL QUALITY STANDARDS FOR RADIOPHARMACEUTICALS FOR POSITRON-EMISSION TOMOGRAPHY

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The current state of quality standards for radiopharmaceuticals (RPs) for positron-emission tomography (PET) is assessed considering primarily national and global requirements for pharmacopoeial practice. The need to develop both general pharmacopoeial standards for RPs for PET and specific monographs for separate pharmaceuticals is established. Common approaches to standardization of each quality indicator are proposed considering known features of PET RPs using dosage forms for parenteral administration as examples.

Keywords: radiopharmaceuticals, positron-emission tomography, nuclear medicine, pharmacopoeia.

Nuclear medicine (NM) is a contemporary thrust of medicine that uses radionuclides and their radioactive decay for diagnosis and therapy in various areas of scientific and practical medicine. It is noteworthy that greater than 50% of the radionuclides produced per year around the world are utilized in nuclear medicine. Radiopharmaceuticals (RPs) are a special group because greater than 95% of the preparations used in Russia are domestically manufactured [1]. The government has recently actively assisted the development and dissemination of NM methods around the country. For example, significant resources and facilities have been directed toward creating new positron-emission tomography (PET) centers.

Radionuclides (RNs) for PET are β^+-emitters with half-lives from several seconds to several hours (^{11}C, ^{13}N, ^{15}O, ^{18}F). The PET method consists essentially of producing a three-dimensional image of the concentration of β^+-emitters using detectors positioned around a circle with the object (patient) placed in the center of it [2].

Quality control of PET RPs has its own specifics that must be considered. In particular, PET RPs, like other RPs, are produced in small batches and are designed for use only in specialized clinics with high-technology equipment; special ventilation, plumbing, and storage systems; radiation protection systems for personnel,; radioactive contamination control systems;, and specially trained personnel. Batches rather often consist of 3 – 5 packages. Also, the shelf life of such RPs can be from several minutes to several days. Therefore, quality control should use methods capable of reliable assessments of the minimal number of samples [1].

Also, Federal Law No. 61-FZ, part 5, art. 13 states that RPs prepared directly in medical institutions are not subject to state registration as usually established by the authorized federal executive body. This in addition to the lack of corresponding pharmacopoeial monographs (PMs) hinders state control and oversight of the quality.

Thus, development of the corresponding quality standards for PET RPs is crucial. In turn, they should help to improve the quality system and facilitate increasing their safety.

The requirements of GPM. 1.11.0001.15 “Radiopharmaceutical preparations” defines a list of quality indicators with which RPs manufactured industrially and/or prepared in medical institutions should comply [3]. PET RPs should comply with these same requirements.

About 10 PET RPs are currently registered in Russia. They all are manufactured in dosage forms for parenteral administration. The most common of them is [^{18}F]-fluorodeoxyglucose ([^{18}F]-FDG) solution for i.v. injection.

The present study addressed the characteristics of the quality indicators specific to this group of preparations that

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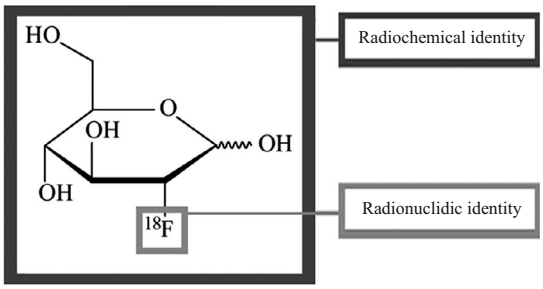

Fig. 1. Structural formula of [^{18}F]-fluorodeoxyglucose.

could have their own peculiarities because all registered PET RPs are manufactured in dosage forms for parenteral administration.

Description. The appearance and main organoleptic and other properties of the preparation (aggregate state, color, transparency, etc.) are indicated [2, 3].

Identity. The indicator should confirm the presence of the declared radionuclide in the declared chemical form. As a rule, gamma or beta spectrometry is adequate to determine the identity of the radionuclide. However, the decay half-life must also be determined for PET RPs. Chromatographic methods or specific chemical reactions are used to determine the radiochemical identity [3, 5, 6].

Transparency, color, mechanical inclusions. These indicators are not controlled in leading global pharmacopoeias because the methods of the corresponding GPMs, the volumes used, and the sampling methods are not calculated for RPs with small batch sizes. They are more often informative in nature and not analytical requirements. The corresponding information is given in the section Description or Labeling. For example, the Fludeoxyglucose F-18 Injection (Fig. 1) monograph in the US Pharmacopeia indicates in the Description a "Clear, colorless solution, free from visible particulates" and in the Labeling section "Do not use if cloudy or if it contains particulate matter" [4 – 7].

Moreover, the potential hazard from using RPs not assessed for these indicators can be critical. Therefore, these indicators should be suitably reflected in the PM and regulations. One method could be delayed control when test results may be obtained after the RP is administered.

pH. The pH value can be determined by ion measurements, acidity or basicity tests, or suitable indicator strips. The last method is preferred considering the small volume of PET RPs and their short half-lives because it is rapid and requires several μL of solution. Modern indicator strips can determine pH values rather accurately to less than ±0.5 units.

Radionuclidic purity (RNP) or impurities (RNIs). This indicator determines the limiting content of radionuclidic impurities and the minimum content of the declared radionuclide (RN). The value of this parameter varies during the shelf life of the preparation because the radionuclides have different half-lives. Therefore, RNIs with half-lives greater than that of the declared radionuclide must be determined. In this instance, it should be indicated that the test results can be obtained after the preparation is administered [2, 5].

The requirements for RNP are determined for two main reasons. First, the imaging method is based on recording the characteristic gamma-radiation of the main RN. The presence of other RNs with different gamma-radiations degrades the image resolution in gamma cameras. Second, the presence of RNIs increases patient radiation burdens.

The standards can be given in two ways depending on the name:

1. An indication of the lower limit of RNP on a certain date and, if necessary, the time. For example, "The F-18 activity should be greater than 99.9% of the total activity."

2. An indication of the upper limit of RNIs on a certain date and, if necessary, the time. For example, "The I-131 activity should be less than 0.1% of the total activity." As a rule, this refers to those impurities that could be formed during preparation of the RP [6, 8].

Radiochemical purity (RCP) or impurities (RCIs). This indicator determines the limiting content of radiochemical impurities and the minimum content of the declared radionuclide in the declared chemical form. The test is performed using various analytical methods such as HPLC, GC, paper chromatography, TLC, and electrophoresis. The distribution of the activity in the chromatogram is determined after and during the separation. The measurement method depends on the nature of the radiation and the separation method. The amounts of tested compounds are incredibly small because radioactive detectors are highly sensitive. Therefore, special attention should be paid to uncertainties when assessing the analytical results. Sometimes, addition of a carrier for the main compound or impurities can reduce the uncertainty. However, in this instance, the risk of the carrier reacting with the RPIs leading to their underestimation arises. HPLC or GC is used if simple chromatographic methods cannot satisfactorily assess the declared compound [8].

In turn, an HPLC method may not always be more informative. For example, a European Pharmacopoeia monograph on [^{18}F]-FDG where HPLC and TLC methods are used states for the latter, "The method allows determination of partially or fully acetylated derivatives of [^{18}F]-FDG and [^{18}F]-2-deoxy-2-fluoro-D-mannose…," which are hydrolyzed under HPLC conditions [6].

The standards can be given in two ways depending on the name:

1. An indication of the lower limit of RCP. For example, "Total activity of [^{18}F]-FDG and [^{18}F]-2-deoxy-2-fluoro-D-mannose should be greater than 95% of the total ^{18}F activity."

2. An indication of the upper limit of the RCIs. For example, "The total [^{18}F]-fluoride activity and partially or fully acetylated derivatives of [^{18}F]-FDG and [^{18}F]-2-deoxy-2-fluoro-D-mannose should be less than 5% of the total ^{18}F activity" [6].

Chemical impurities. This indicator determines the limiting content of chemical impurities regardless of their radioactivity. The test is used if these compounds are present because of the synthesis technology. The RCP cannot be judged

from this indicator because even if a preparation is practically chemically pure it may contain impurities with high specific activities (small amounts of impurities can be highly active and constitute an unallowable fraction of the total activity).

In general, chemical impurities are determined if they:

are toxic;

affect the studied physiological processes;

give undesired physicochemical or chemical reactions.

Special attention should be paid to pharmacologically active impurities even in especially small amounts (e.g., receptor ligands). If necessary, the indicator Stereoisomeric Purity can be included [3, 8].

Residual organic solvents. The contents of residual organic solvents must be controlled depending on the specifics of the PET RP production technology. The test can be performed after the RP is administered because of the time required for it. The allowed standards should be ensured by the validated production technology.

Sterility. PET RPs, like other RPs for parenteral injection, should be prepared observing safeguards in order to exclude microbial contamination and to ensure sterility. Sterility testing is conducted according to GPM Sterility. However, as a rule, the analytical results for sterility are obtained after an actual batch is used because of the short half-lives of the radionuclides incorporated into most RPs. However, sterility testing is sometimes not conducted, e.g., because of a limited batch size. In such situations, the preparation is administered to a patient using a membrane filter in the stream. The used process technology should be validated as appropriate [3].

Bacterial endotoxins or pyrogenicity. Tests for Bacterial Endotoxins are preferred for RPs because of the high sensitivity and rapid performance [2]. The Bacterial Endotoxins section indicates the limiting content of bacterial endotoxins calculated for the maximum preparation dose in mL considering its administration pathway. The limiting bacterial endotoxin contents of each component are calculated for preparations prepared from lyophilizates and solutions (eluates) considering the limiting content of bacterial endotoxins in the final dosage form. The limiting bacterial endotoxin contents for i.v. administered preparations are calculated using the formula 175 EU/*V*, where *V* is the maximum preparation dose in mL at the end of the shelf life (greatest volume of preparation dose with the lowest activity) [3].

Activity. The activity of an RN in a preparation is indicated on a certain date and time (accurate to the minute if the RN half-life is less than 1 d) and is expressed in Bq. The specific activity is expressed in Bq/g of substance; molar activity, in Bq/mol of substance; and volume activity, in Bq/mL of preparation [3, 5 – 7].

Maximum recommended dose per mL (V). A certain preparation dose in activity units must be administered to achieve a diagnostic effect. The preparation activity decreases because of the expected decay of the RN so that the required volume for injection increases. The maximum injected volume in mL (*V*) should be determined for all RPs. The standards should be adjusted to this volume, which allows the static (constant) standard to be established and the total injected volumes to be controlled [3 – 5]. Standardization of the limiting content of RCIs and chemical impurities per *V* is recommended.

The assessment of the current state of PET RP quality standards showed that the corresponding pharmacopoeial standards are currently given in leading global pharmacopoeias. However, the State Pharmacopoeia, XIVth Ed., includes only one GPM that is applied to all RPs. Also, PET RPs have several peculiarities that require separate general pharmacopoeial standards for them and the corresponding special PMs. This becomes especially critical considering that the RP market in Russia is mainly represented by national manufacturers.

Requirements of existing GPMs for dosage forms, analytical methods, and separate quality indicators should definitely be considered in drafting such standards. General requirements for all analytical methods should include primarily their reliability with minimum analysis times because of the limited shelf lives of PET RPs and their small batch sizes. Also, test results for several indicators can be obtained even after the preparation is administered. Indicators such as Transparency, Color, and Mechanical Inclusions may require special methods and approaches that provide for working with radioactivity and small sample sizes.

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