GUIDELINE FOR

QUALITY ASSURANCE AND QUALITY CONTROL OF

^{18}F-FDG (2-Deoxy-2-fluoro-D-glucose)

Forum for Nuclear Cooperation in Asia (FNCA)
Cyclotron and Positron Emission Tomography (PET) in Medicine

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This guideline summarizes Quality Assurance (QA) and Quality Control (QC) of ^{18}F-FDG and is issued as an outcome by sub-group 2 (PET Radiopharmaceuticals) of FNCA Cyclotron and PET in Medicine.
Since a general guideline on ^{18}F-FDG injection is already developed in each participating country, it is rather difficult to develop a single guideline for all. For that reason, we would like to entrust each country to develop a specific protocol for each module.

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CONTENTS **PAGE**

1 INTRODUCTION

1. 1 Scope of this document

Positron emission tomography (PET) is a medical imaging modality involving the use of a unique type of radiopharmaceutical drug product. The majority of PET drug products are injected intravenously into patients for diagnostic purposes. Most PET drugs are produced using cyclotrons at locations that are proximately to the patients to whom drugs are administered.

Under section 501 (a) 92) (B) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 351 (a) (2) (B)), a drug is adulterated if the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to ensure that the drug meets the requirements of the act as to safety and has the identity and strength, and meets the quality and purity characteristics, that it purports or is represented to posses.

In the clinical application of PET radiopharmaceuticals, it is essentially important to assure the safety of the product. Many guidelines for the production of PET radiopharmaceuticals have been published in each country or regions such as found in the United State Pharmacopoeia (USP), European Pharmacopoeia (EP) and Japanese Standard. Precise procedures for the production of PET radiopharmaceuticals and their Quality Assurance (QA)/Quality Control (QC) are described in the guidelines. There are some minor discrepancies found among the guidelines. Each guideline does not preclude the use of an alternative if it is equivalent or better to the method described in the guideline.

The scope of this document is to focus on the QA/QC of [^{18}F]-FDG as a result achieved from the FNCA 2009 Workshop on Cyclotron and Positron Emission Tomography (PET) in Medicine held in Kuala Lumpur. As a guide to the preparation of document, the Japanese standard “Standards for Compounds Labeled with Positron Nuclides Approved as Established Techniques for Medical use (by the Subcommittee on Medical Application of Cyclotron-Produced Radionuclides) (2001 revision)” and “Description of the Established Standard Techniques of Labeling Compounds with

Positron Nuclides for use as Radiopharmaceuticals: approved by the Subcommittee on the Medical Application of Cyclotron-Produced Radionuclides (revised in 2001)" are referred.

1.2 Objectives of this guideline

The objectives of this guideline are:

a) To provide a general knowledge and procedures to perform the QA/QC of PET radiopharmaceutical.
b) To assure the safety of product before released for clinical application.
c) To develop a minimum QA/QC tests data required for the production of [^{18}F]-FDG PET radiopharmaceutical as a pioneer guideline to further provide other guidelines for other types of ^{18}F label compounds.

The minimum requirements of quality assurance and quality control for the preparation of [^{18}F]-FDG would be estimated and this Guideline should be read in conjunction with all related rules and regulations enforced.

2 QUALITY ASSURANCE (QA)

2.1 General

Quality Assurance is a wide ranging concept which covers all matters which individually or collectively influence the quality of product. It is the sum total of the organized arrangements made with the object of ensuring that medicinal products are of the quality required for their intended use. Quality Assurance therefore incorporates quality control and some aspect of cGMP requirements plus other factors outside the scope of this Guideline.

2.2 Principles

There shall be a management system to oversee preparations to ensure that a PET radiopharmaceutical of sufficient quality is prepared. It is essential to examine, approve or reject components, containers, closures, in-process materials, packaging materials, labelling, and finish**ed** product to ensure compliance with procedures and specifications affecting the identity, concentration, quality and purity of a PET radiopharmaceutical.

In consideration of the unique nature of PET drugs and PET drug production, the cGMP requirements for PET drug products are the following:

a) Fewer required personnel with fewer organizational restrictions consistent with the scope and complexity of operations;
b) Allowance for multiple operations (or storage) in the same area as long as space for other controls are adequate;
c) Streamlined requirements for aseptic processing consistent with the nature of the production process;
d) Streamlined quality control requirements for components;
e) Self-verification of significant steps in PET drug production consistent with the scope and complexity of operations;
f) Same-person oversight of production, review of batch records, an authorization of product release consistent with the scope and complexity of operations;
g) Specialized quality control requirements for PET drugs produced in multiple sub-batches; and

h) Simplified labelling requirements consistent with the scope and complexity of operations.

These provisions reflect the unique characteristics of PET drug production, shall make it easier for PET centers to achieve compliance with cGMP requirements.

2.3 Quality Control

PET drug product producers shall have a quality control arrangement that has the responsibility and authority to oversee production operations to ensure that each PET drug product meets the requirements of safety and has the identity and strength, and meets the quality and purity characteristics that it is supposed to have according to the standards. Each PET producer shall determine what personnel should staff the quality control unit. At some PET centers, it may be reasonable for the same personnel to be involved in both production and quality control.

The quality control personals shall examine and approve or reject components, containers, closures, in-process materials, packaging materials, labelling, and finished dosage forms to ensure compliance with procedures and specifications affecting the identity, strength, quality, or purity of a PET drug product.

2.4 Standard of [^{18}F]-FDG

A radiopharmaceutical that is an aqueous injection containing fluorine-18 included within the 2-deoxy-2-fluoro-D-glucose structure. This injectable can include 2-deoxy-2-fluoro-D-glucose as carrier containing 90 – 110% of the fluorine-18 radioactivity labelled on the molecule at the assay day. Specific activity of this injectable solution reaches more than 200 MBq in 1 mg of 2-deoxy-2-fluoro-D-glucose on the assay day and time.

2.5 Current Good Manufacturing Practice for PET Drugs

Current good manufacturing practice for PET drug products is the minimum requirements for the methods to be used in, the facilities and control used for, the production, quality control, holding, or distribution of PET drug products intended for human use. This regulation is applicable only to the manufacturer or production of PET drug products and in this document, it refers to the [^{18}F]-FDG product. Any human drug

product that does not meet the definition of a PET drug product must be manufactured in accordance with the current good manufacturing requirements such as the Guide to Good Manufacturing Practice For Medicinal Products in the PIC/S GMP Guide.

Current good manufacturing practice for PET drugs must address certain matters to ensure that each drug product meets the requirements of the act that to safety and has the identity and strength, and meets the quality and purity characteristics, that it is supposed to have. These matters are:

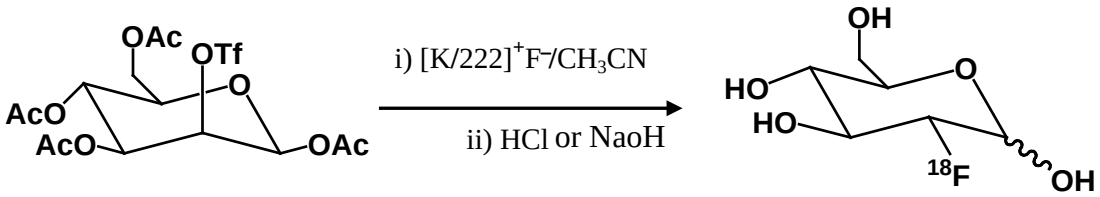
a) Personnel and resources
b) Quality control system
c) Facilities and equipments
d) Control of components, in-process materials, and finished products
e) Production and process controls
f) Laboratory controls
g) Acceptance criteria
h) Labelling and packaging controls
i) Complaint handling; and
j) Record keeping

3 PRODUCTION OF FLUORINE-18 (^{18}F)

This radiopharmaceutical is prepared by using fluorine-18 obtained by irradiating neon-20 with deuteron or oxygen-18 with proton. Due to its simplicity of managing the process, most cyclotron centers currently use oxygen-18 as their target material. The manufacturing of 2-Deoxy-2-fluoro-D-glucose (^{18}F) is then performed. After the purification, the injection solution is prepared.

4 GENERAL REMARKS ON SYNTHESIS OF [^{18}F]-FDG

2-Deoxy-2-fluoro-D-glucose (^{18}F) Injection has been synthesized according to the following reaction scheme:



Mannose triflate

[^{18}F]-FDG

It is then purified by passing through a series of purification column AG 50W-X8 column, AG 11A8 column, Sep-Pak C18 cartridge and Sep-Pak alumina N cartridge, and then sterilized by passing through a 0.22 μm sterile membrane filter. Various modifications of the fluoride ion method developed by Hamacher et al. are available to prepare [^{18}F]-FDG, which are classified to the type of catalyst used, hydrolysis condition, purification technique and the use of on-column method. Therefore, the impurities contained in the product would be different and depending on the method used. Originally, [^{18}F]-FDG were produced by [^{18}F]F_2 method or [^{18}F]acetyl hypofluorite method containing a small amount of F_2 gas, but [^{18}F]fluoride methods not-adding carrier became predominant over the original [^{18}F]F_2 method and have been used in most of the PET facilities. Therefore, the quality control method relating to the previous methods adding carrier were not the subject of discussion in this guideline.

[^{18}F]-FDG have been produced in the various category PET facilities such as at the university hospital, research centers, dispensing centers, etc. Thus the requirements criteria for the QA/QC of the [^{18}F]-FDG may differ from one organization to others, which shall depend on the scale, activity and mission of each facility. In this guideline,

the sub-group 2, named as PET Radiopharmaceutical Group at the 2009 FNCA Workshop on Cyclotron and PET In Medicine meeting agreed that the requirement criteria for the QA/QC of [^{18}F]-FDG is categorized into a GMP-facility and into a non-GMP facility.

5 GENERAL TESTS

General tests described in this Guideline should be conducted according to the General tests described in "The Minimum Requirements for Radiopharmaceuticals", "The Japanese Pharmacopoeia", "The United State Pharmacopoeia" and "The European Pharmacopoeia" and other authorized standards. This chapter describes only Gamma-ray Determination, Bacterial Endotoxins Test and Sterility test which tests are not common in usual PET facilities where QA/QC should be conducted in a very short time by a small number of staff.

5.1 Gamma-ray Determination

Gamma-ray Determination measures gamma and X-rays out of radiation rays emitted from radionuclides. The measurement uses a gamma spectrometer which is used for identifying radionuclides, detecting radionuclidic impurities and determining their radioactivities.

5.1.1 Measurement of gamma-ray spectrum

This measurement identifies nuclides and detects radionuclide impurities using gamma spectrometer through measuring and comparing gamma-ray spectrum of radiopharmaceutical and calibration standard of the radionuclide.

Operation method

Unless otherwise specified, the operation is conducted as follows;

Take an accurately measured aliquot of a radiopharmaceutical and a calibration standard in separate containers. Add solvent as required to achieve the concentration of 4 – 400 kBq/mL. Place the identical amount (0.1 – 10 mL) of it into containers of the identical material and shape. Seal the containers and label as a specimen and a standard. Make sure that the measurement devices and volumes are identical.

Place the test specimen and the standard at a set distance from the gamma-ray detector, and measure gamma-ray spectrum. When the standard is the same radionuclide as that in the radiopharmaceutical, make sure that all the energy peaks of gamma-rays in the specimen's spectrum ("gamma-ray peak" hereafter) match the gamma-ray peaks of the standard, when determining radionuclides.

When using a specimen with a different radionuclide from that in the radiopharmaceutical, use the gamma-spectrum of the standard for energy calibration, and obtain the energy level of gamma-ray peaks for the specimen's spectrum to determine the radionuclides.

5.1.2 Assay using a gamma spectrometer

This method conducts assay through calculating the counting rate of the typical gamma-peak region emitted from the radiopharmaceutical and the standard sample.

Operation method

Unless otherwise specified, the operation is conducted as follows;

When the standard is the same radionuclide as that in the radiopharmaceutical, use the gamma-spectrometer to measure gamma-ray spectrum and calculate the counting rate of the gamma peak region for the specimen and the standard. Use the formula below to obtain the radioactivity (A_c) in a set aliquot of radiopharmaceutical. Radioactivity in a set aliquot of radiopharmaceutical:

$$A_c = S \times (A/B) \times (D/D') \times G$$

In the above formula, A and B represent the measured value of counting rates (corrected for background region) for the same energy peak region of the specimen and the standard D and D' represent the dilution factors for the radiopharmaceutical and standard respectively. S is radioactivity for a set amount of the standard. G is the geometric correction factor on the positions of the specimen and the standard, and should be equal to 1 wherever possible.

When the standard is the different radionuclide, use the gamma-spectrometer to measure gamma-ray spectrum, and use the energy and gamma-ray emission rate of the

radionuclide use as the standard to work out the spectrometer's energy peak counting efficiency ("efficiency" hereafter). Measurement conditions for a radiopharmaceutical must be identical to those for the standard. Use the radiopharmaceutical's gamma-ray spectrum obtained to calculate of the target gamma peak region (N_x). The radioactivity for a set aliquot of the radiopharmaceutical (A_c) may be obtained with the formula below, using the efficiency (F_x) pre-determined with the standard:

$$A_c = [(N_x/F_x)] \times D \times G$$

In this formula, R represents the ratio of gamma ray emission, while D represents the dilution factor of the radiopharmaceutical. G is the geometric correction factor on the positions of the spectrum and the standard, and should be equal to 1 wherever possible.

5.1.3 Half-life measurement

This method takes the assay using a gamma spectrometer, well-type scintillation counter or ionization chamber.

Unless otherwise specified, the operation is conducted as follows;

Operation method

a) Using a decay curve

Take a set aliquot of the radiopharmaceutical immediately after preparation, and use a radioactivity measuring device (well-type scintillation counter, ionization chamber, etc.) to determine chronological changes in radioactivity under the same measuring or geometrical conditions. Plot the logarithm with time on the horizontal axis and radioactivity (or meter readings with the background corrected) on the vertical axis, and confirm that the decay curve obtained forms a straight line. Use the straight line to work out the time required for radioactivity to fall by half.

b) Two-point determination

Take a set aliquot of the radiopharmaceutical immediately after preparation, and use a radioactivity measuring device (well-type scintillation counter, ionization chamber,

etc.) to determine radioactivity twice under the same measuring or geometrical conditions. The second measurement should be taken after a half-life period of the applicable nuclide elapses. If the applicable radionuclides's half-life period is too short or too long to facilitate measurement, the second measurement may be conducted after a ¼ of the half life, or 3 times the half life. Use the formula $T = 0.693 \times t/\ln (A_0/A)$ to obtain the half-life T, whereby A_0 and A represent the radioactivity (or meter readings with the background corrected) at the first and second measurement respectively, and t represents the interval between the two measurements.

When a decay curve is used to measure the half-life, confirm the half-life of the candidate nuclide when the plotted value indicates 95 to 105% that of the target radionuclide used. When the bracketing approach is used for measuring the half-life of radionuclides, confirm the half-life of the nuclide used when plotted value indicates 90 to 110% of the half-life of said nuclide.

5.2 Bacterial Endotoxin Test

Bacterial Endotoxin Test is designed to detect bacterial endotoxins based on the blood-clotting reaction that occurs when bacterial endotoxins, derived from Gram-negative bacteria, activate the blood cell component LAL (Limulus amebocyte lysate) derived from horseshoe crabs (Limulus polyphemus or Tachypleus tridentatus) or related organism. Said test may be conducted with one of the following techniques; the Gel-clot technique based on clot formation, turbidimetric technique based on turbidity changes, or chromogenic technique based on color presentation from hydrolysis of the chromogenic substrate. If the result is inconclusive, use the Gel-clot technique to make final judgment. Note that gel-clotting of LAL may be triggered with a certain type of polysaccharide.

Conduct this test promptly to avoid contamination from microorganisms.

Apparatus

Wash glassware thoroughly with water, and heat it to a minimum of 250 ^{0}C in 30 minutes to inactivate endotoxins before use in the test.

Preparation of sample solution

Unless otherwise specified, adjust a sample solution to pH 6.0 to 8.0 with either 0.1 mol/L sodium hydroxide or 0.1 mol/L hydrochloric acid for use in the test, when and where applicable.

Preparation of standard endotoxin stock solution

Add endotoxin-testing water to standard endotoxin in a vial to make up a solution with 10,000 endotoxin units (EU) in 1.0 mL, and shake well to facilitate complete dissolution. The just prepared standard endotoxin stock solution is immediately stored at 2 – 8 ^{0}C, and should be used within 14 days of preparation.[Note 1]

Preparation of standard endotoxin solution

Rigorously shake the standard endotoxin stock solution, and place it in cold water. Measure a designed aliquot of the stock accurately and add endotoxin-testing water to prepare a standard endotoxin solution with the endotoxin concentration specified for the radiopharmaceutical injection used in testing. Keep the solution in cold water, and use within 90 minutes of preparation.

5.2.1 Gel-clot technique

LAL solution

LAL is freeze-dried amebocyte lysate from horseshoe crabs (Limulus polyphemus or Tachypleus tridentatus). Add endotoxin-testing water to LAL, with constant stirring to facilitate dissolution before storage in ice water until use. This series of procedures may be omitted if a single-testing LAL reagent is available in a vial or ampoule.

Operational procedures

Place 0.10 mL each of LAL solution in three test-tubes (each with 10-mm inner diameter and 75-mm length, and add 10 mL each of sample, standard endotoxin solution or endotoxin-testing water separately to the test-tubes, respectively. In cases where the

single-testing LAL reagent is available in vials or ampoules, add the sample solution, standard endotoxin solution or endotoxin-testing water to the vials or ampoules directly.

Place a cap on the test tubes, and mix the solution gently before standing at 37 ± 1 ^{0}C for 60 ± 2 minutes.

Judgement

Tilt the respective test tubes containing the sample, standard endotoxin solution and endotoxin-testing water 180 degrees gently without stirring the contents, and observe the solutions, accordingly. The endotoxin test is considered positive if the content agglutinates without physical distorting, but is otherwise negative.

The test is considered conformed when the test tubes treated with the sample solution and endotoxin-testing water test negative while that treated with the standard endotoxin solution tests positive.

If either the test tube treated with endotoxin-testing water tests positive, or that treated with standard endotoxin solution tests negative, the test is deemed invalid.

In such cases, use new reagents or replace the equipment, and repeat the test.

Note: 1: Perform preliminary tests to confirm neither the reaction is promoted nor inhibited by the sample solution in said test.

5.2.2 Optical techniques

a) Turbidimetric technique

This technique observes the changes in turbidity associated with the clotting protein “coagulin”, which is formed in the reaction between endotoxin and LAL, and assesses the changes in light penetration. The interval it takes for the sample reaction to display specific turbidity from the start of the reaction is taken as the gel-clotting time (Tg). Since a calibration relationship between endotoxin concentration and Tg can be derived, the said technique can therefore quantitatively measure endotoxin.

LAL solution

Add endotoxin-testing water to a vial of LAL gently with constant stirring to facilitate dissolution, and chill the preparation in ice water until use. In cases where a single-test lyophilized LAL reagent is packed in a vial or ampoule, the procedure may be omitted.

Operational procedures

Measure three volumes of 0.10 mL each of LAL solution and place each sample separately in a test-tube. Add 0.10-mL samples each of endotoxin-testing water, standard endotoxin solution or sample solution to the tubes, respectively. In cases where the single-testing LAL reagent is available in vials/ampoules, add the sample solution, standard endotoxin solution or endotoxin-testing water to the vials/ampoules directly.

Place a cap on the test tubes, and mix the solution gently before standing at 37±1°C. Measure the time it takes light penetration to attain and remain constant at a certain level.

b) Chromogenic technique

The synthetic substrate technique uses a compound (e.g. Box-Leu-Gly-Arg-pNA) to bind synthetic peptides (with an amino acid sequence similar to coagulogen hydrolysate) with chromophore p-nitroaniline (pNA). This amidase activity of the endotoxin-activated clotting enzyme promotes pNA release. This endotoxin content is measured using colorimetry (at 405-nm absorbance). The time required to release pNA is inversely propotional to the endotoxin content, and the logarithmic correlation between time and endotoxin concentration shows linearity. This linear plot affords quantitative measurements of the endotoxin content.

LAL

Mix LAL with synthetic substrate, and add 0.2 mol/L Tris-HCl buffer (pH 8.0) before stirring gently to facilitate dissolution. Store the treated LAL solution in ice water until use.

Operational procedures

Treat three 0.10 mL samples each of LAL solution with synthetic substrate in separate test-tubes (each with 10-mm inner diameter and 75-mm length). Place mixtures in the 3 test-tubes in ice water, and add 0.10 mL each of sample solution, standard endotoxin solution and endotoxin-testing water to the respective test-tubes. Close each test tube with a cap, agitate the mixture and heat at 37 ^{0}C for a fixed period of time (30 minutes). Immediately transfer and chill the tubes in ice water after heating, add 0.4 mL of acetic acid solution (0.08 mol/L) to terminate the reaction. Measure the mixtures in endotoxin-testing water at 405-nm absorbance within 2 hours after terminating the reaction.

Judgement

Except for spirally administered preparation, an endotoxin concentration below 175 EU/V in non-oral preparations is considered negative, where V represents the highest volume in mL administered in 1 hour.

The sample is considered conformed when treatment with the sample solution and endotoxin-testing water in the test-tubes yields a negative result, as well as when treatment with standard endotoxin solution in the test-tube tests positive.

If treatment with endotoxin-testing water tests positive, or if treatment with standard endotoxin solution tests negative, the test is deemed invalid.

Use new reagents or replace equipment to repeat the test.

5.3 Sterility Test

Sterility test may be conducted pursuant to the general tests described in the Japanese Pharmacopoeia, or in the blood culture system.

5.3.1 Blood culture system

This system examines bacterial presence in a sample through observing the flow of culture medium from the culture bottle to the growth signal reservoir, connected with a thin needle, reflecting a rise in the culture bottle’s positive pressure as a result of bacterial metabolism producing gaseous compounds.

This system consists of a blood bottle and growth signal reservoir.

Culture bottle

The culture bottle contains culture medium that can simultaneously grow aerobic and anaerobic bacteria.

Measurement method

1) Volume of test solution

Although this system is capable of conducting measurement with 0.1 to 10 mL of test solution, use at least 1 mL. Note that a test sample diluted over 100 times cannot be used as test solution.

2) Operational method

a) Remove the bottle's plastic cap, and use swab alcohol to thoroughly disinfect the rubber stopper.
b) Gently agitate the sample and culture medium to mix them well.
c) Place the inoculated culture bottle in an incubator at 35 – 37 ^{0}C for approximately 1 hour.
d) Use alcohol cotton balls to thoroughly sterilize the culture bottle's rubber stopper.
e) Remove the cap from the growth signal connector needle, making sure not to touch the needle itself. Insert the needle into the culture bottle's rubber stopper, and equalize the pressure inside the bottle (negative pressure), before inserting the needle further until the end reaches the culture medium.
f) Press down the fixed external cylinder, and affix the growth signal reservoir to the bottle.
g) Place the reservoir-affixed bottle ("signal unit" hereafter) in the incubator, and conduct machine shaking at least four times on Day 1. From Day 2 onwards, conduct shaking twice a day.
h) Observed the signal unit according to the following schedule:
    i. Measure once each at 2 hours later and 6 hours later on Day 1, day 2 (24 hours later), Day 3 (48 hours later), Day 4 (72 hours later) and Day 8 (7 days later).
    ii. The measurement schedule for 2 hours later (Day 1) may be omitted.

iii. Conduct the following operations if the culture medium appears cloudy at the time of observation.

i) Gently shake the bottle to mix the contents.

j) Place the nozzle of a syringe (5 mL or over) with the needle removed at the ventilation hole on the cap of the growth signal reservoir, and inject air into the signal unit. Remove the syringe to let the culture medium flow into the growth signal reservoir.

k) Remove the cap of the growth signal reservoir, and collect the culture medium into a sterile syringe.

l) Repeat the operations a) – h). Add at least 5 mL of culture medium.

Judgement

Give a positive result if the culture medium is above the fixed external cylinder of the growth signal reservoir. Give a negative result if the culture medium does not reach the fixed external cylinder of the growth signal reservoir even on Day 8, and if the medium does not appear cloudy. If the medium appears cloudy, conduct the operation i) – l) to continue culturing, and make a judgment on Day 8.

6 ANALYSIS METHODS FOR [^{18}F]-FDG INJECTION

An alternative analysis method may be used if the method is deemed to yield higher levels of accuracy and precision than those specified here.

6.1 Radiochemical purity

Radiochemical purity is determined by monitoring the radioactivity signal from the detector coupled in series with HPLC or by measuring the radioactivity distribution with radioactivity scanners or imagers after TLC separation.

High Performance Liquid Chromatography (HPLC)[Note 1]

a) Column: μBondapak Carbohydrate (3.9 mm- inner diameter x 300-mm length), Waters [Note 2].
   Elution phase: CH_3CN/H_2O (85:15)
   Flow rate: 2 mL/min
   Retention time: 3.8 minutes

b) Column: Asahipak NH2P-50 4E (4.6-mmm inner diameter x 250-mm length), Showa Denko.
   Elution phase: CH_3CN/ H_2O (9:1)
   Flow rate: 2 mL/min
   Retention time: 5.9 minutes

c) Column: Aminex HPX-87H (7.8-mm inner diameter x 300-mm length), Bio-Rad [Note 3].
   Elution phase: H_2O (85^0C)
   Flow rate: 1 mL/min
   Retention time: 7.0 minutes

[Note 1]: A regular analysis requires only one set of conditions. However, in cases where the reaction criteria are required to be examined or in the event of a problem, it is preferable to use two sets of conditions with different characteristics in the analysis. Note that the [^{18}F] fluoride ion is absorbed on a column and not eluted in a system adhere a buffer solution is not used as an elution phase, and [^{18}F] fluoride ion is not included in the elution phase passing through the regular alumina column (alumina cartridge).

[Note 2]: Residual radioactive impurities which appear in the case of insufficient hydrolysis, can be well separated from [^{18}F]-FDG under Condition (c), but not under Condition (a).

[Note 3]: Bio-Rad HPX 87C column may be used in a similar manner.

Thin Layer Chromatography (TLC)

a) Plate: Silica gel (soaked in 0.2 mol/L NaH_2PO_4, dried at the room temperature, and heated at 110 ^{0}C for 30 minutes before use).
Elution phase: methanol/triethylamine (1000:1)
Rf value: 0.62

b) Plate: Silica gel (soaked in 0.2 mol/L NaH_2PO_4, dried at the room temperature, and heated at 110 ^{0}C for 30 minutes before use).
Elution phase: acetonitrile/H_2O (95:5)
Rf value: 0.4

c) Plate: Cellulose, Merck
Elution phase: 2-butanol/conc. NH_4OH/H_2O (6: 1 : 33)
Rf value: 0.67

d) Plate: Silica gel (soaked in 0.2 mol/L NaH_2PO_4, dried at the room temperature, and heated at 110 ^{0}C for 30 minutes before use).
Elution phase: isopropanol/H_2O (4 : 1)
Rf value: 0.70

e) Plate: Silica gel (soaked in 0.2 mol/L NaH_2PO_4, dried at the room temperature, and heated at 110 ^{0}C for 30 minutes before use).
Elution phase: 2-butanol/CH_3OH/CH_3CO_2H (3 : 1 : 1)
Rf value: 0.76

6.2 Chemical purity and specific radioactivity

High Performance Liquid Chromatography (HPLC)

A high-sensitivity electrochemical detector is required to gauge the specific radioactivity of [^{18}F]-FDG synthesized by the carrier-free fluoride ion method. Said detector should be able to conduct high-sensitivity saccharide analysis in amperometric mode (e.g. detectors from Japan Dionex or Yokokawa Analytical System, etc.). Quantitative limit for [^{18}F]-FDG is 30 to 50 ppb.

However, tests for calculating specific radioactivity may be omitted for preparations that have been manufactured by non-carrier added method and where quantification of mass is impractical.

a) Column: Dionex CarboPac PA1 (4-mm inner diameter x 250-mm length), Japan Dionex.
   Elution phase: 0.1 mol/L NaOH
   Post-column reagent: 0.35 mol/L NaOH
   Flowrate: 1ml/L/min for both elution phase

b) Column: CarboPac PA-1(4.0 mm inner diameter x 250 mm, Dionex) + CarboPac PA-1 guard (4.0 mm inner diameter x 50 mm), 30 ^{0}C.
   Elution phase: 200 mM NaOH
   Flow rate: 0.3 mL/min
   Detection: pulsed amperometry, electrode, gold (working) vs Ag/AgCl (reference)
   Retention time: 20.0 min (FDG), 21.0 min (ClDG (2-Deoxy-2chloro-D-glucose))

6.3 Chemical Impurities

Kryptofix 222

The method using TLC is convenient to detect Kryptofix 222 during the manufacturing of [^{18}F]-FDG using the fluoride ion method. The detection limit is around 30 ppm.[Note 1]

Thin Layer Chromatography (TLC)

a) Plate: Silica Gel
   Elution phase: CH_3OH/conc. NH_4OH (9 : 1)
   Rf value: Kryptofix 222, 0.38;
   [^{18}F]-FDG, 0.83

b) Plate: Silica gel
   Elution phase: triethylamine/CH_3OH (0.1 : 99.9)
   Rf value: [^{18}F] fluoride ion,
   Kryptofix 222, 0.38;
   glucose, 0.36;
   [^{18}F]-FDG, 0.62

[Note 1]: Kryptofix 222 is rarely detected during manufacturing under normal conditions, if the positive ion-exchange resin AG50W-X8 is used for purification.

Tetrabutyl ammonium (TBA) ion

The following test is required when tetrabutylammonium bicarbonate ($TBAHCO_3$) is used as a reaction catalyst.

To prepare the standard reagent solution, take a designed aliquot of 0.1 to 0.5 mL of 1 mmol/L standard TBA ion solution, add 3 mL of 3.75 mmol/L sodium bis (cis-1,2-diethylenedithiolate) nickelate solution, 1 mL of 0.1 mmol/L acetate buffer (pH 5) and water to make a final volume of 5 mL before standing for 20 minutes. Next, add the standard reagent solution to a separating funnel containing 10 mL chloroform, mix throughly, separate the lower chloroform phase, and filter with a teflon filter paper to remove water moisture. Use a spectrophotometer to measure the absorbance at 318-nm wavelength and plot a calibration graph thereof. Measure the absorbance of a 1-mL sample, after adjusting it with the same procedure. Based on the calibration graph, the TBA ion concentration of the material is then derived.

Aluminium ion

The following test is required when the alumina column (alumina cartridge) is used to purify [^{18}F]-FDG[Note 1].

Drip a drop of [^{18}F]-FDG solution on a test plate, and make sure it turns purple when treated with one drop each of ammonia reagent and alizarin sulfonate solution without turning red when acidified with acetic acid. The detection limit is around 0.65 mg (ca. 0.02 ppm).

The measurement range of commercially available ion-test paper Alumicheck (Advantek Toyo) is 2 – 100 ppm.

[Note 1]: Aluminium ion is not detected when [^{18}F]-FDG preparation is neutral under normal conditions.

Methanol, ethanol, acetonitrile

The type of residual solvents contained in the [^{18}F]-FDG injection strongly depends on the production method. Ethanol and acetonitrile are commonly contained in the solution, but methanol and ether are in the rare case. Here, an example listed in the Japanese standard is described.

Column: HP-PLOT Q (0.52-mm inner diameter x 30 m, 40 μm, Agilent, 160 ^{0}C)
Carrier: helium. 4 mL/min
Detection: FID, 250 ^{0}C
Injection; 0.5 mL, split (2 : 1), 250 ^{0}C
Retention time: 2.4 min (methanol)
4.2 min (ethanol)
5.0 min (acetonitrile)

7 QUALITY CRITERIA AND FREQUENCY OF TEST FOR [^{18}F]-FDG

The quality criteria of [^{18}F]-FDG are slightly different among the countries. The level of QA/QC may depend on the scale and the object of the facility, number of staff and so on. The following criteria and frequency of the test summarised in Table 1 are categorized in a GMP facility and In-house facility, and has been agreed and accepted by the member of Group 2 at the FNCA Workshop on Cyclotron and Positron Emmission Tomography (PET) in Medicine, 20 November 2007 held in Kuala Lumpur, Malaysia.

Table 1: Quality Criteria of [^{18}F]-FDG and Frequency of Tests

No.	QC Tests	Acceptance Criteria	Frequency of Test	
			GMP-facility	In-house
1	Appearance	Clear, colorless or slightly yellow	Every Batch	Every Batch
2	pH	5.0 – 8.0	Every Batch	Every Batch
3	Radionuclidic Identity	Half-life: 105 – 115 min	Every Batch	Every Batch
4	Radiochemical Purity	> 95% (Radio-TLC)	Every Batch	Every Batch
5	Kryptofix 2.2.2	< 50 μg/mL	Every Batch	Every Batch
6	Residual Solvents	< 0.04% acetonitrile < 0.5% alcohol < 0.5% ether	Every Batch	Twice a year
7	Bacterial Endotoxins	150 EU/V	Every Batch	Every Batch
8	Sterility	Meet the Test	Every Batch	Every Batch
9	Membrane Filter Integrity	>50 psi	Every Batch	Not necessary
10	Radionuclidic Purity	>99.5% (511, 1022 keV)	Twice a year	Not necessary
11	Specific Radioactivity	No carrier added	Not necessary	Not necessary
12	ClDG	< 1.0 mg/V	Once a year	Not necessary
13	Aluminium Ion	< 10 μg/mL	Not necessary	Not necessary
14	Osmolarity	-	Not necessary	Not necessary

8 REFERENCES AND FURTHER READING

1. Standard for Compounds Labeled with Positron Nuclides Approved as Established Techniques for Medical Use (by the Subcommittee on Medical Application of Cyclotron-Produced Radionuclides) (2001 revision).
2. Description of the "Established Standard Techniques of Labeling Compounds with Positron Nuclides for use as radiopharmaceuticals: Approved by the Subcommittee on Medical Application of Cyclotron-Produced Radionuclides (revision in 2001).
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   http://www.jrias.or.jp/index.cfm/6,784,108,145,html
3. Guide to Good Manufacturing Practice For Medicinal Products in the PIC/S GMP Guide, 2007.
4. Current Good Manufacturing For Positron Emission Tomography, http://www.fda.gov.
5. Guidelines on the Current Good Radiopharmacy Practice (cGRPP) In the Preparation of Radiopharmaceuticals, cGRPP-Guideline, Version 2 March 2007.
6. Guidelines for Good Manufacturing Practices of Radiopharmaceuticals, IAEA, RAS/2/2009 on Quality Assurance and Good manufacturing Practices for Radiopharmaceuticals, 2001

9 TERMINOLOGY

i. Acceptance Criteria means numerical limit, ranges, or other criteria for tests that are used for or making a decision to accept or reject a unit, lot, or batch of a PET drug product.

ii. Batch means a specific quantity of PET drug intended to have uniform character and quality, within specified limits, that is produced according to a single production order during the same cycle of production.

iii. Component means any ingredient intended for use in the production of a PET drug product, including any ingredients that may not appear in the final PET drug product, such as precursor, reagent, and solvents.

iv. Final release means the authoritative decision to permit the use of a batch of a PET drug in humans.

v. PET means positron emission tomography

vi. PET center means a facility that is engaged in the production/application of a PET drug product.

vii. PET drug means a drug that exhibits spontaneous disintegration of unstable nuclei by the emission of positrons and is used for providing dual photon positron emission tomographic diagnostic images.

viii. PET drug product means a finished dosage form that contains a PET drug, whether or not in association with one or more other ingredients.

ix. PIC/S means the Pharmaceutical Inspection Co-operation Scheme

x. Production means the manufacturing, compounding, processing, packaging, labelling, reprocessing, repacking, relabeling, and testing of a PET drug product.

xi. Quality control means a system for maintaining the quality of PET drug product, intermediate, analytical supplies, and other components, including container-closure systems and in-process materials, through procedures, tests, analytical methods, and acceptance criteria.

xii. Specifications means the tests, analytical procedures, and appropriate acceptance criteria that establish the criteria to which a PET drug, PET drug product, component, or other material used in PET drug production must conform to be considered acceptable for its intended use. Conformance to specifications means that a PET drug, PET drug product, when tested according to the described analytical procedures, meets the listed acceptance criteria.

FNCA 2009 WORKSHOP ON CYCLOTRON AND PET IN MEDICINE
NAME OF GROUP 2: PET RADIOPHARMACEUTICAL

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