Comparison of Various Requirements of the Quality Assurance Procedures for ^{18}F-FDG Injection*

Joseph C. Hung, PhD

Nuclear Medicine, Department of Radiology, Mayo Clinic, Rochester, Minnesota

The quality assurance (QA) requirements (i.e., test procedure, acceptance criteria, and testing schedule) for fludeoxyglucose ^{18}F (^{18}F-FDG) injection listed in the U.S. Pharmacopeia (USP); the draft Chemistry, Manufacturing, and Controls (CMC) issued by the U.S. Food and Drug Administration (FDA); and the European Pharmacopeia (EP) were compared. The FDA Modernization Act of 1997 requires that the QA of compounded PET drug products be in compliance with the PET compounding standards and official monographs included in the USP. However, the "sunset" clause of the PET section within the FDA Modernization Act of 1997 stipulates that all PET drug products, in due course, must meet the requirements for drug approval procedures and current good manufacturing practice, and the FDA has issued a draft CMC that includes QA specifications for ^{18}F-FDG injection. The purpose of this article is to discuss the pros and cons of each of the QA tests stated in the USP, CMC, and EP and to propose a practical testing method for each required test, thereby helping end users to ensure the quality of the ^{18}F-FDG injection product. It is hoped that this article will stimulate further cooperation among various countries worldwide in the development of a set of harmonized and sensible QA standards for all PET drug products.

Key Words: ^{18}F-FDG injection; quality assurance; U.S. Pharmacopeia; Chemistry, Manufacturing, and Controls; Food and Drug Administration; European Pharmacopeia

J Nucl Med 2002; 43:1495–1506

A pharmacopeia is an authoritative source for the quality assurance (QA) of any drug product. In the United States, the U.S. Pharmacopeia (USP) is recognized as an official compendium and is referenced in various statutes (*1*). The QA standards described in the USP-published monographs for each drug product have served to standardize procedures, thereby helping to ensure drug quality and to protect public health.

Section 121 of the U.S. Food and Drug Administration (FDA) Modernization Act of 1997 requires that the FDA establish approval procedures and current good manufacturing practice (CGMP) for PET drugs (*2*). The 1997 FDA Modernization Act instituted an amendment to the Federal Food, Drug, and Cosmetic Act in which a compounded PET drug is deemed to be adulterated if it is compounded, processed, packed, or held other than in accordance with the PET compounding standards and the official monographs of the USP (*2*).

In establishing the approval procedures for PET drugs, the FDA issued a draft Chemistry, Manufacturing, and Controls (CMC) section concerning 3 PET drug products (i.e., ammonia ^{13}N injection, fludeoxyglucose ^{18}F [^{18}F-FDG] injection, and sodium fluoride ^{18}F injection). The section contains a subsection that deals with regulatory specifications, standard testing procedures, and testing schedules (*3*).

In addition to the USP, the European Pharmacopeia (EP) also includes QA standards in the form of monographs for several PET drug products (*4*). Presently, the Japanese Pharmacopeia has not established standards for any PET drug products.

Although stipulating the acceptance criteria and testing procedures for drugs, the USP does not specify the frequency of QA tests. A possible reason is that the USP tests are commonly used either for challenging certain claims made by consumer organizations or, by government regulators, for evaluating marketed drug products (*5*). However, specification of testing schedules can help end users to ensure that necessary QA tests begin at an appropriate time and to know whether a drug can be released before the completion of the tests.

Because ^{18}F-FDG injection is the most commonly used PET radiopharmaceutical, the discussion of QA procedures in this article focuses on this drug. A careful examination of 3 official sources (i.e., USP, CMC, and EP) for information on ^{18}F-FDG revealed significant discrepancies between the 3 sets of QA standards for PET drugs (*1,3,4*). This article compares the pros and cons of the information in the 3

Received Mar. 13, 2002; revision accepted Jul. 16, 2002.

For correspondence or reprints contact: Joseph C. Hung, PhD, Nuclear Medicine, Department of Radiology, Mayo Clinic, 200 First St., SW, Rochester, MN 55905-0001.

E-mail: jhung@mayo.edu

*NOTE: FOR CE CREDIT, YOU CAN ACCESS THIS ACTIVITY THROUGH THE SNM WEB SITE (http://www.snm.org/education/ce_online.html) THROUGH NOVEMBER 2003.

official sources and proposes specifications, procedures, and testing schedules for each QA requirement for ^{18}F-FDG injection. It is hoped that this article will promote the development of a set of harmonized and practical QA standards for ^{18}F-FDG injection and other PET drug products.

The QA test items listed in this article were taken from the USP, CMC, and EP (*1*,*3*,*4*) and are listed in random order. Various QA tests were incorrectly categorized in the USP, CMC, and EP under the wrong QA test item (*1*,*3*,*4*). These misplaced QA tests have been rearranged in this article to correspond to the appropriate QA test items.

To provide readers with an overall perspective of the QA requirements described in the 3 official documents (i.e., USP, CMC, and EP), a brief, collective description of each test procedure, set of acceptance criteria, and testing schedule (or testing frequency) is included in each QA test section. After each description is a discussion that includes personal comments and suggestions on various QA test issues. Each QA test section concludes with an outline for a proposed QA test (i.e., abbreviated test procedure, acceptance criteria, and testing schedule, if applicable).

The QA test items considered and described in this article are appearance, identification (radionuclidic identity and radiochemical identity), purity (radionuclidic purity, radiochemical purity [RCP], and chemical purity), radiochemical impurity, assay for radioactivity, specific activity, pH, residual solvents, bacterial endotoxins, sterility, osmolality, glucose, stabilizer, and membrane filter integrity.

APPEARANCE

USP. Unlisted.

CMC. The solution must be colorless and free from particulate matter when observed visually behind leaded glass under adequate light. The test must be completed before release of the drug product.

EP. The solution appearance must be clear, colorless, or slightly yellow.

Comments. The USP should include appearance testing in the official monograph for ^{18}F-FDG injection because the USP section titled "Labeling" implicitly requires that a visual inspection be performed before product release (*1*). However, if the product is viewed through a tinted thick leaded glass window, the color of the solution may be obscured, and it would be difficult to note a colorless appearance of ^{18}F-FDG. To examine the true color of ^{18}F-FDG solution, one should view the product through nontinted leaded glass.

In my experience, ^{18}F-FDG injection must be clear and colorless. A yellow or straw color, if observed, is probably an impurity generated during the ^{18}F-fluoride ($^{18}F^-$) production process.

The EP places the appearance test under a subsection titled "Character" along with the following statement: "Fluorine-18 has a half-life of 109.8 min and emits positrons with a maximum energy of 0.633 MeV, followed by annihilation gamma radiation of 0.511 MeV" (*4*).

Proposed Test. The solution must be clear, colorless, and free of particulate matter. If possible, the solution must be viewed through nontinted leaded glass under adequate light. The test must be completed before release of the drug product.

RADIONUCLIDIC IDENTITY

USP. The half-life, determined using a suitable detector system, is between 105 and 115 min.

CMC. The half-life, determined by measuring the radioactivity decay of the sample over a 10-min period, is between 105.0 and 115.0 min. The test must be completed before release of the drug product.

EP. There is no specific test listed for radionuclidic identity in the EP. However, tests A and B in the section titled "Identification" appear to refer to the determination of radionuclidic identity: (A) The only γ-photons have an energy of 0.511 MeV. Depending on the measurement geometry, a sum peak of 1.022 MeV may be observed. (B) Measurement of half-life, determined with a suitable instrument, is between 105 and 115 min. The ^{18}F-FDG injection may be released for use before completion of this test.

Comments. The USP does not include a time period for measuring the half-life of ^{18}F; however, the CMC gives a count period of 10 min (*1*,*3*). Nevertheless, it is not clear how critical the count time is in determining the physical half-life of ^{18}F. The section of the EP titled "Radiopharmaceutical Preparations" states that the half-life must be measured "at intervals usually corresponding to half of the estimated half-life throughout a time equal to about 3 half-lives." (*6*). The reasons for tracking the count time up to 3 or 4 half-lives of the radioisotope of interest are to ensure that one can properly calculate any deviation in the measured half-life and to better estimate other potential radioisotope contaminants (Capintec, Inc. [Pittsburgh, PA], written communication, January 2002). Consequently, the EP allows ^{18}F-FDG injection to be released for use before completion of the radionuclidic identity and purity testing, because it will take 6–8 h (i.e., 3 or 4 half-lives of ^{18}F) to properly determine the half-life of ^{18}F (*4*,*6*). However, my experience has shown that a count time of at least 10 min provides a relatively accurate value for ^{18}F half-life; at least, the value regularly falls within the range quoted by the USP, CMC, and EP (*1*,*3*,*4*).

In the EP, radionuclidic identity and radiochemical identity testing have been placed into a section titled "Identification," which is the same format as that used in the USP (*1*,*4*). However, the EP fails to state whether each of the 3 tests listed is performed to evaluate radionuclidic identity or radiochemical identity (*4*).

With a major peak at 0.511 MeV and a possible sum peak of 1.022 MeV on a γ-ray spectrum, both of which are features common to a positron emitter and, as such, prop-

erties not unique to the ^{18}F radioisotope, it is inappropriate to use examination of the γ-ray spectrum as a test to determine radionuclidic identity. Hence, item A in the identification section of the EP must not be used to identify ^{18}F radioisotope (*4*).

Proposed Test. The measured half-life is between 105 and 115 min, as obtained with a suitable detector to determine radioactivity decay over an appropriate time (e.g., 10 min). The test must be completed before release of the drug product.

RADIOCHEMICAL IDENTITY

USP. The relative front (or retention factor) (R_f) value of ^{18}F-FDG injection corresponds to the R_f value of the USP ^{18}F-FDG reference standard solution (~0.4) obtained with the RCP test.

CMC. The R_f of ^{18}F-FDG injection corresponds (±10%) to the R_f (~0.4) of the ^{18}F-FDG reference standard, when both are chromatographed together side by side on the same thin-layer chromatography (TLC) strip impregnated with silica gel (SG). The activated TLC SG plate is developed in acetonitrile:water (95:5, v/v) and then scanned using a radiochromatographic TLC scanner. The test must be completed before release of the drug product.

EP. No radiochemical identity test is specified in the EP. However, test C listed in the section titled "Identification" appears to be for the determination of radiochemical identity (*4*). The principal peak on the radiochromatogram (i.e., test "a" for RCP) obtained with high-performance (or high-pressure) liquid chromatography (HPLC) for the test solution has approximately the same retention time as the principal peak on the chromatogram obtained with the reference solution.

Comments. The TLC method is accurate and reliable; however, as with most TLC techniques, the R_f will vary according to different plate brands or operating conditions (*7*). Consequently, a radiochemical is best identified when a pure, authentic sample of the compound in question is used as a reference on the same chromatogram. In addition, although both test and standard solution samples are spotted on the same TLC strip, the R_f values measured for the test substance may differ from the values obtained for the reference compound (*7*).

To verify the resolution and reproducibility of the chromatographic system (e.g., gas chromatography [GC] or HPLC), system suitability must be tested before sample analysis (*7*,*8*). The difference in measured R_f values between the test samples and reference samples should not exceed reliability estimates determined statistically from replicate assays (*7*). Application of the same principles of system suitability to the TLC method before sample analysis would be prudent to validate its precision and effectiveness.

It is interesting to note that although 3 USP reference standards (i.e., USP fludeoxyglucose, USP fludeoxyglucose related compound A RS, and USP fludeoxyglucose related compound B RS) are identified in the USP (*1*), as far as I am aware, these USP grade reference standards cannot be obtained from any commercial source.

As stated earlier, the EP combines both radionuclidic and radiochemical identity testing under a section titled "Identification," the same format as that used by the USP (*1*,*4*). However, the EP fails to state whether each of the 3 tests listed is for evaluation of radionuclidic identity or for evaluation of radiochemical identity.

The EP test for radiochemical identity (i.e., test "C" in the "Identification" section) is associated with the following drawbacks: The suggested HPLC system is more expensive and elaborate than the TLC system; the HPLC system is not widely available in nuclear medicine or nuclear pharmacy laboratories; and HPLC requires 2 runs (i.e., one using the test solution and another using the reference solution) whereas TLC requires only a single run (i.e., sample and reference standard are spotted on the same TLC SG plate).

Proposed Test. The R_f value of ^{18}F-FDG injection corresponds, within an acceptable range (determined by system suitability testing), to that of the ^{18}F-FDG reference standard solution when both are chromatographed side by side on the same TLC SG strip, which is developed in acetonitrile:water (95:5, v/v) and then scanned using a radiochromatographic scanner. The test must be completed before release of the drug product.

RADIONUCLIDIC PURITY

USP. No less than 99.5% of observed γ-emissions on a γ-spectrum, obtained with a suitable γ-ray spectrometer, should correspond to the 0.511-MeV, 1.022-MeV, or Compton scatter peaks of ^{18}F.

CMC. γ-Spectroscopy of decayed sample. Acceptability limit and testing schedule must be included.

EP. The γ-ray spectrum must be recorded using a suitable instrument. The measured half-life is between 105 and 115 min. ^{18}F-FDG injection may be released for use before completion of the test.

Comments. It is not clear whether the phrase *decayed sample* in the CMC refers simply to a radioactive sample being decayed or if the word *decayed* is intended to suggest that the sample must be counted over time (*3*). Additionally, the CMC gives no specific information on acceptable photopeaks (i.e., 0.511 MeV, 1.022 MeV, or Compton scatter) for the radionuclidic purity testing. Why the CMC does not include the acceptability limit and testing schedule for the radionuclidic purity test is unclear (*3*). Possibly, the FDA may view the radionuclidic identity test as a potential candidate for a reduced testing schedule (e.g., initial validation, with annual testing thereafter). This reduction may, in turn, be due to the costly equipment (i.e., multichannel analyzer) that is needed for radionuclidic purity testing. More important, the radionuclidic impurity outcome may not be crucial

to patient welfare or imaging quality, making the test academic relative to release of the drug product.

Determining physical half-life does not allow one to quantify the radionuclidic purity of a radionuclide. The use of physical half-life to test the radionuclidic purity of a radioisotope, as stated in the EP, is incorrect and should not be included (*4*). If the EP adopts the use of a γ-ray spectrum for the radionuclidic purity test, the statement "^{18}F-FDG injection may be released for use before completion of the test" must be removed (*4*), because completing a γ-spectroscopic evaluation with a multichannel analyzer takes approximately only 10–15 min.

Proposed Test. No less than 99.5% of the observed γ-emissions on a γ-spectrum obtained with a suitable γ-ray spectrometer should correspond to the 0.511-MeV, 1.022-MeV, or Compton scatter peaks of ^{18}F. An initial validation must be performed, followed by annual testing.

RCP

USP. No less than 90.0% of the radioactivity of ^{18}F-FDG injection as determined by an activated TLC SG plate developed in a mixture of acetonitrile and water (95:5, v/v).

CMC. No less than 90% of the radioactivity of ^{18}F-FDG injection locates at R_f ~0.4 of an activated TLC SG plate developed in a mixture of acetonitrile and water (95:5, v/v). The test must be completed before release of the drug product.

EP. For the HPLC method, radioactivity of ^{18}F-FDG and 2-^{18}F-fluoro-2-deoxy-D-mannose (FDM) is no less than 95% of the total radioactivity, of which ^{18}F-FDM fraction does not exceed 10% of the total radioactivity. For the TLC method, no less than 95% of the radioactivity of ^{18}F-FDG injection locates at R_f ~0.45 of an activated TLC SG plate developed in a mixture of acetonitrile and water (95:5, v/v).

Comments. Same comments as those in the "Radiochemical Identity" section with regard to the use of the TLC system.

It seems excessive that the EP requires 2 testing methods (i.e., HPLC and TLC) for the evaluation of RCP of ^{18}F-FDG injection (*4*). It would be more sensible to state that either of 2 specified testing methods (i.e., HPLC or TLC) may be used to determine the RCP of ^{18}F-FDG injection. Nevertheless, the TLC method is preferable, as described in the "Radiochemical Identity" section. Although the HPLC method described in the EP has the potential to separate ^{18}F-FDG from ^{18}F-FDM, an epimer of ^{18}F-FDG, in my experience, the chromatographic resolution is poor (*4,9–11*). In addition, HPLC conditions used in the EP procedure will cause the level of nonhydrolyzed or partially hydrolyzed 2-^{18}F-fluoro-2-deoxytetraacetyl-D-glucose to be either underestimated or overlooked. Under the suggested HPLC conditions, these intermediate reaction products may further hydrolyze to the desired end product (*4*).

The HPLC method stated in the EP sets a minimal acceptance limit for both ^{18}F-FDG and ^{18}F-FDM at 95%, of which the fraction of ^{18}F-FDM cannot exceed 10% of the total activity (*4*). This statement implies that the RCP threshold for ^{18}F-FDG can be as low as 85% (i.e., 95% of ^{18}F-FDG and ^{18}F-FDM – 10% of ^{18}F-FDM = 85% of ^{18}F-FDG)—a value contrary to the minimal acceptance limit set for ^{18}F-FDG (i.e., 95%) in the TLC method section (*4*). Unlike the HPLC section, the TLC section of the EP does not specify a minimal acceptance limit for the other radiochemical impurities (e.g., ^{18}F-FDM).

The isomeric purity test for ^{18}F-FDM is performed using the HPLC method described in the EP (*4*). However, this test is not required either in the USP or in the CMC. The use of acid hydrolysis reduces the potential for epimerization of ^{18}F-FDG to ^{18}F-FDM such that one may argue that the isomeric purity test is not necessary for ^{18}F-FDG injection prepared using acid hydrolysis (*12*). However, formation of ^{18}F-FDM using alkaline hydrolysis is a possibility at elevated temperatures (*9–11*). Interlab studies of ^{18}F-FDG samples, prepared using alkaline hydrolysis at room temperature, have demonstrated that ^{18}F-FDM exists at undetectable levels (*11*). For institutions using alkaline hydrolysis, performing this test periodically may be sensible.

Because the EP implements 2 inconsistent RCP acceptance limits (i.e., 85%–95% for HPLC and 95% for TLC) and both the USP and the CMC use an identical threshold, a minimal RCP acceptance limit of 90% is suggested in the proposed test.

Proposed Test. No less than 90.0% of the radioactivity of ^{18}F-FDG injection locates at the spot that corresponds, within an acceptable range (e.g., ±10%), to that of the ^{18}F-FDG standard solution, when both are chromatographed together side by side on the same TLC SG strip, which is developed in acetonitrile:water (95:5, v/v) and then scanned using a radiochromatographic scanner. The test must be completed before release of the drug product.

If alkaline hydrolysis is used for the preparation of ^{18}F-FDG injection, the fractions of ^{18}F-FDG and ^{18}F-FDM radioactivity must be determined, and the fraction of ^{18}F-FDM should not exceed 10% of the total radioactivity. An initial validation must be performed, followed by annual testing.

RADIOCHEMICAL IMPURITY

USP. The radiochemical impurity testing requirement is not listed as a stand-alone QA item as in the CMC but, rather, is included within the "Radiochemical Purity" testing section. The fraction of $^{18}F^-$ does not exceed 10% of the total radioactivity of an ^{18}F-FDG injection, in accord with the requirements in the USP "Radiochemical Purity" section.

CMC. No more than 4.0% of $^{18}F^-$ radioactivity must be present in an ^{18}F-FDG injection. The test must be completed before release of the drug product.

EP. The requirements for radiochemical impurity are listed in the "Radiochemical Purity" section, in which the fractions of $^{18}F^-$ and ^{18}F-FDM cannot exceed 5% and 10%,

respectively, of the total radioactivity of an ^{18}F-FDG injection.

Comments. The 4% $^{18}F^-$ limit stipulated in the CMC (*3*) should have some validity. Inclusion of an $^{18}F^-$ specification is essential if exceeding a certain level of $^{18}F^-$ may affect image quality or generate a high radiation dose. According to the USP, an ^{18}F-FDG injection may contain up to 10% free $^{18}F^-$ and still be acceptable, whereas the EP sets the free $^{18}F^-$ threshold in an ^{18}F-FDG injection at 5% (*1*,*4*).

Proposed Test. If the 4% limit of $^{18}F^-$ is not required for an ^{18}F-FDG injection, then the requirement for testing to detect free $^{18}F^-$ must be removed. Otherwise, no more than 4% of the radioactivity of $^{18}F^-$ should locate at the origin of an activated TLC SG plate developed in a mixture of acetonitrile and water (95:5, v/v). The test must be completed before release of the drug product.

If a valid reason exists for the inclusion of an $^{18}F^-$ threshold, this requirement can easily be incorporated into the "Radiochemical Purity" section using such wording as "No less than 90.0% of the radioactivity of ^{18}F-FDG injection (R_f ~0.4) and no more than 4% of the radioactivity of $^{18}F^-$ (R_f ~0.0) as determined by an activated TLC SG plate developed in a mixture of acetonitrile and water (95:5, v/v)."

ASSAY FOR RADIOACTIVITY

USP. Use of a properly calibrated system to determine the radioactivity in MBq (or mCi)/mL of the ^{18}F-FDG injection.

CMC. Use of a properly calibrated system to determine the total radioactivity in millicuries, as well as the concentration of radioactivity in mCi/mL, at the end of the synthesis. The test must be completed before release of the drug product.

EP. Use of a suitable counting instrument, as determined either by comparison or calibration with a standardized ^{18}F solution, to measure the radioactivity.

Comments. Although curies or millicuries are the units of radioactivity commonly used in the United States, becquerels are the internationally recognized unit for radioactivity. Therefore, including megabecquerels and MBq/mL in the CMC specification would be sensible. Because the photon energy of ^{137}Cs (i.e., 662 keV) is close to 511 keV, and ^{137}Cs is widely used as a reference source for calibration of a dose calibrator, it may not be necessary to use a standardized ^{18}F solution to calibrate the most commonly used counting device (i.e., dose calibrator), as stipulated in the EP (*4*).

Proposed Test. Use of a suitably calibrated system to determine the total radioactivity of the ^{18}F-FDG injection in megabecquerels (or millicuries) and the radioactivity concentration in MBq/mL (or mCi/mL). The test must be completed before release of the drug product.

SPECIFIC ACTIVITY

USP. No carrier is added.

CMC. No carrier is added. No specific testing procedure is listed, provided the drug product is prepared by a no-carrier-added method of synthesis. No testing is performed.

EP. Unlisted.

Comments. The CMC section does not require that the specific activity be determined before release of the ^{18}F-FDG injection.

Proposed Test. No carrier is added. No testing for specific activity of the ^{18}F-FDG injection is required if it is prepared by a no-carrier-added method of synthesis. If a carrier-added synthesis is used for the production of ^{18}F, an appropriate test, acceptance criteria, and the testing frequency for the specific activity must be defined.

pH

USP. 4.5–7.5.

CMC. The pH limits must be specified. pH paper with pH reference standards is used to determine the pH value of the ^{18}F-FDG injection. The test must be completed before release of the drug product.

EP. 4.5–8.5

Comments. According to the USP <791> "pH" section, test paper may be suitable for the measurement of an approximate pH value (*13*). Because the ranges of pH limits for ^{18}F-FDG injection stipulated in the USP and EP are quite broad (*1*,*4*), use of narrow-band pH paper (e.g., color change for each 0.5 pH unit) should be adequate for checking the pH value of ^{18}F-FDG injection. The accuracy and traceability of pH paper should initially be verified with standard pH buffers. In any case, the measured value for pH obtained using pH paper is approximate, and the accuracy is probably no better than ±0.25 pH units (*14*).

The reason for the discrepancy between the USP and the EP with regard to the acceptable pH range is unclear (*1*,*4*). The CMC allows end users to specify acceptable pH limits for ^{18}F-FDG injection.

Proposed Test. An acceptable pH range should not affect the stability of ^{18}F-FDG injection and should minimize patient discomfort during administration. The pH level must be determined using a suitably calibrated pH measuring device in conjunction with pH reference standards. The test must be completed before release of the drug product.

CHEMICAL PURITY

Each test, with the associated limits described in this section, must be performed when that chemical substance is either used or formed en route during synthesis of the ^{18}F-FDG injection. Both the USP and the EP indicate that the methods and limits for chemical purity may be disregarded if the substances described are not used or cannot be formed during production (*1*,*4*). However, for methods of synthesis that may result in chemical substances (e.g., chemical impurities, unlabeled ingredients, reagents, and by-products) that are not listed below, the USP requires the control and measurement of any potential toxic substances (*1*).

Aminopolyether

USP. The size and intensity of the spot obtained from the test solution does not exceed those obtained from the USP reference standard solution (i.e., 50 μg/mL aminopolyether – USP fludeoxyglucose related compound A RS). The TLC SG plate is developed in a mixture of methanol and 30% ammonium hydroxide (9:1, v/v).

CMC. The size and intensity of the TLC spot obtained from the test solution does not exceed those obtained from the standard solution (i.e., 50 g/mL Kryptofix 222). The test must be completed before release of the drug product.

EP. The intensity of the spot obtained from the test solution does not exceed that obtained from the standard solution (i.e., 2.2 mg/V, where V is the maximum recommended dose, in mL). The TLC SG plate is developed in a mixture of methanol and ammonia (9:1, v/v).

Comments. In my experience, the TLC test for detecting aminopolyether (*15*,*16*) can be unreliable. The spot development is sometimes indistinct; however, an alternative method does exist (*17*).

The CMC incorrectly lists the concentration of the reference solution of Kryptofix 222, an aminopolyether complex (i.e., 50 μg/mL, instead of 50 g/mL) (*3*). In addition, the CMC fails to provide a detailed testing procedure (e.g., mobile phase is not mentioned).

The EP testing method is similar to the USP method for aminopolyether, with the exception of the mobile phase (i.e., EP: ammonia; USP: 30% ammonium hydroxide) (*1*,*4*). However, the EP test does not require a comparison of spot sizes (*4*). Because the aminopolyether test is essentially a comparative intensity spot test between the product and the reference, the EP is correct in not requiring a comparison of spot sizes (*4*). In addition, the EP indicates that the testing of aminopolyether "is performed only on the bulk solution before addition of sodium chloride by the producer and it is not intended for the final preparation to be injected" (*4*).

In contrast to the USP and the CMC, the EP acceptance limit is set at 2.2 mg per V, where V is the maximum recommended dose, in milliliters (*4*). Accordingly, it will take a volume of 44 mL ^{18}F-FDG injection to reach the threshold limit of 50 μg/mL stipulated in the USP and possibly in the CMC (in the event that 50 g/mL is a typographic error) (*1*,*3*). Without a doubt, the limit for aminopolyether stated in the EP is considerably higher than the thresholds set in the USP and CMC (*1*,*3*,*4*). Also, the concentration of aminopolyether standard solution specified in the EP must be adjusted in accordance with the volume of the maximum recommended dose of ^{18}F-FDG injection (*4*), whereas the concentration of aminopolyether standard solution described in the USP and possibly in the CMC is fixed (i.e., 50 μg/mL) (*1*,*3*). Because the recommended dose for ^{18}F-FDG injection may vary between PET centers, it is advisable to remove the word *recommended* from the QA statement in the EP (*4*).

Why the acceptance limits for aminopolyether in the USP, CMC, and EP are so different is not clear (*1*,*3*,*4*). It is important to ensure that any chemical substances with potential toxic, physiologic, or pharmacologic effects are within an appropriate limit, which is probably established on the basis of the median lethal dose (LD_{50}). The LD_{50} is defined as any dose that kills 50% of the test animals, and it is a standardized measure for expressing and comparing the toxicity of chemicals.

For aminopolyether, the intravenous LD_{50} in rats is 35 mg/kg (*18*), which is much less than the LD_{50} value of the 2 potentially toxic residual solvents (i.e., intravenous LD_{50} in rats for acetonitrile and dehydrated alcohol, 1,680 and 1,440 mg/kg, respectively) (*19*,*20*). As a result, the threshold for aminopolyether stipulated in the USP may be a more sensible value to use (*1*). However, this does not mean that the aminopolyether limit stipulated in the EP is incorrect (*4*). If the EP has used a valid reason in justifying the higher threshold for aminopolyether, the aminopolyether limit stated in the EP would be more suitable. It would be sensible to establish the acceptability of the amount of aminopolyether based on the mass of aminopolyether in a maximum dose volume administered to a patient, rather than basing this acceptability on the concentration of aminopolyether stated in the USP and CMC (*1*,*3*). Nevertheless, the V used to evaluate the aminopolyether limit must be the volume (in mL) of the maximum administered dose that would be dispensed at the expiration time rather than at a time near completion of the synthesis of ^{18}F-FDG injection.

Unless there is a valid reason to support the aminopolyether limit required by the EP (*4*), the proposed test for aminopolyether agrees with the more restrictive threshold for aminopolyether (to be on the safer side) stipulated in the USP and possibly in the CMC (*1*,*3*).

Proposed Test. The intensity of the spot obtained from the test solution does not exceed that obtained from the standard solution (e.g., 50 μg/mL aminopolyether). The TLC SG plate is developed in a mixture of methanol and 30% ammonium hydroxide (9:1, v/v). The test must be completed before release of the drug product.

2-Chloro-2-Deoxy-D-Glucose (ClDG)

USP. No more than 1.0 mg ClDG is found in the total volume of the batch of ^{18}F-FDG injection produced. The test is performed with an HPLC system.

CMC. No more than 1.0 mg ClDG is found in the total volume of the batch of ^{18}F-FDG injection produced. The test is performed with an HPLC system. An initial validation must be performed, followed by annual testing.

EP. No more than 0.5 mg ClDG is found in the maximum recommended dose of ^{18}F-FDG injection, in milliliters. The test is performed with an HPLC system.

Comments. Acid hydrolysis of crude FDG or the use of anionic exchange resins in the chloride form may potentially result in the formation of ClDG (*1*,*9*). The test procedure, requiring a highly sensitive method of detection for the HPLC system (*1*,*9*), is expensive and therefore not practical for use in most production facilities. In addition, a

system suitability test for the HPLC method must be performed to verify that the system provides adequate resolution and reproducibility for the analysis (*1*,*7*,*8*). The USP stipulates that the resolution of peaks corresponding to FDG and ClDG standard reference solutions should not be less than 1.5, and the relative SD for replicate injections should not be more than 5% (*1*). The EP, which also uses an HPLC method (with a suitable detector for carbohydrate analysis), indicates that the corresponding peaks of FDG and ClDG may not be completely resolved (*4*). In my experience, I have not been able to successfully separate the ^{18}F-FDG and ClDG peaks. Because of the potential for difficulty in obtaining isolated peaks for FDG and CLDG, the EP therefore allows the use of a summation of peak areas that correspond to FDG and ClDG for the assessment of the QA requirement for FDG and ClDG (*4*). This requirement states that the areas of the FDG and ClDG peaks should not be greater than the areas of peaks corresponding to FDG or ClDG reference standard solutions (*4*). These constraints may explain why the CMC has implemented a less frequent testing schedule for ClDG (i.e., an initial validation followed by annual testing) (*3*).

The mobile phase, as described in the USP, is 0.2 mol/L NaOH (dissolving 16 g/mL of 50% NaOH solution in 1,000 mL of water) (*1*), whereas the EP method uses 0.1 mol/L NaOH for the mobile phase (*4*). The chemical purity testing for ClDG and FDG, as stipulated in the EP, requires the use of 3 reference standards (i.e., glucose, FDG, and ClDG) (*4*). However, the actual role of the glucose standard solution in the chemical purity testing is not clear. If the reference standard of glucose is used to identify and quantify the level of D-glucose in an ^{18}F-FDG injection, the EP fails to specify an acceptability limit for D-glucose. In the "Chemical Purity" section, the EP incorrectly states that D-glucose is a chemical impurity of ^{18}F-FDG produced through nucleophilic pathways, whereas FDG is generated when electrophilic pathways are used to produce ^{18}F-FDG (*4*). Both D-glucose and FDG are potential chemical impurities of ^{18}F-FDG produced by either nucleophilic or electrophilic pathways.

Nonetheless, the EP uses a more stringent test limit of 0.5 mg per maximum recommended dose, in milliliters (*4*), in contrast to the test limit of both the USP and the CMC (1.0 mg in the total volume of the batch of ^{18}F-FDG injection produced) (*1*,*3*). Because no LD_{50} information for ClDG can be found in the published literature, it is difficult to judge which ClDG acceptable limit—that of the USP, that of the CMC, or that of the EP—is appropriate.

Similar to the previous discussion on the acceptable threshold for aminopolyether, it seems logical to set the ClDG limit on the basis of the mass of ClDG that a patient will receive from a specific volume of the maximum administered dose, rather than basing the limitation on a specific concentration of ClDG in an ^{18}F-FDG injection. Therefore, the threshold of ClDG defined in the EP (i.e., 0.5 mg ClDG per maximum recommended dose, in mL. The word *recommended* must be eliminated, as previously discussed for aminopolyether) (*4*) is more appropriate than the ClDG limit stipulated in the USP and CMC (i.e., 1.0 mg ClDG per total batch volume) (*1*,*3*). However, to include the worst-case scenario of ClDG that may be given to a patient in a dose of ^{18}F-FDG injection, the volume of the maximum administered dose used in the calculation of ClDG must be that which would be dispensed at the expiration time. Similar to the previous discussion with regard to the preparation of standard solution, the EP specification for ClDG requires that the standard solution be diluted to volume V, which may differ at each assay (*4*), whereas the standard solution of ClDG stipulated in the USP and EP is set at a constant value (*1*,*3*).

Proposed Test. No more than 0.5 mg ClDG is found in the maximum dose of ^{18}F-FDG injection, in milliliters, at the expiration time. The test is completed using HPLC with a suitable method of detection. The areas of the FDG and ClDG peaks should not be greater than the areas of peaks corresponding to FDG or ClDG reference standard solutions. An initial validation must be performed, followed by annual testing.

2-Fluoro-2-Deoxy-D-Glucose

USP. Unlisted.

CMC. Unlisted.

EP. No more than 10 mg FDG is found in the maximum recommended dose of ^{18}F-FDG injection, in milliliters. The test is performed using an HPLC system. The areas of the FDG and ClDG peaks should not be greater than the areas of peaks corresponding to FDG or ClDG reference standard solutions.

Comments. The HPLC method stated in the EP is similar to the method for the determination of ClDG, and the acceptance limit of FDG is also expressed in units of weight-in-injection volume (*4*). Because the EP lists both ClDG and FDG under the same section, titled "Chemical Purity" (*4*), the comments on separation of FDG and ClDG peaks, test frequency, mobile phase, reference standard of glucose, recommended dose, and preparation of a standard solution of FDG, stated in the previous section entitled "2-Chloro-2-Deoxy-D-Glucose," also apply to FDG.

Again, no LD_{50} information for FDG can be found in the published literature. It is not clear why the EP has an acceptance limit for FDG, whereas the USP and CMC do not require measurement of this chemical substance (*1*,*3*,*4*). If the QA items for ^{18}F-FDG injection should include the assessment of FDG, a similar requirement, as stated previously for ClDG, should also be implemented for FDG.

Proposed Test. Unless there is some validity for the 10-mg FDG limit stipulated in the EP, performance of this test should not be required before the release of ^{18}F-FDG injection. Otherwise, no more than 10 mg FDG is found in the maximum dose of ^{18}F-FDG injection, in milliliters, at the expiration time. The test is performed using an HPLC system. The areas of the FDG and ClDG peaks should not be greater than the areas of peaks corresponding to FDG or

ClDG reference standard solutions. An initial validation must be performed, followed by annual testing.

Tetra-Alkyl Ammonium Salts

USP. Unlisted.

CMC. Unlisted.

EP. No more than 2.75 mg tetra-alkyl ammonium salts is found in the maximum recommended dose of ^{18}F-FDG injection, in milliliters. The test is performed with an HPLC system.

Comments. Testing is required if tetra-alkyl ammonium salts are used as the phase transfer catalyst. Because tetra-alkyl ammonium salts are not commonly used as a phase transfer reagent, both the USP and the CMC may decide not to include this substance in the "Chemical Purity" section. Refer to the previous sections for a discussion of removal of the word *recommended* and addition of the phrase *at the expiration time*.

Proposed Test. No more than 2.75 mg tetra-alkyl ammonium salts is found in the maximum dose of ^{18}F-FDG injection, in milliliters, at the expiration time. The test is performed using an HPLC system and must be completed before release of the drug product.

4-(4-Methylpiperidino)Pyridine

USP. Unlisted.

CMC. Unlisted.

EP. No more than 0.02 mg 4-(4-methylpiperidino)pyridine is found in the maximum recommended dose of ^{18}F-FDG injection, in milliliters. The test is performed using ultraviolet spectrophotometry.

Comments. This test is required only if 4-(4-methylpiperidino)pyridine is used for the phase transfer catalyst. Again, this compound is not listed in the "Chemical Purity" section of either the USP or the CMC, possibly because it is not widely used as a phase transfer reagent. Refer to the previous sections for a discussion of removal of the word *recommended* and addition of the phase *at the expiration time*.

Proposed Test. No more than 0.02 mg 4-(4-methylpiperidino)pyridine is found in the maximum dose of ^{18}F-FDG injection, in milliliters, at the expiration time. The test may be performed with an ultraviolet spectrophotometer. The test must be completed before release of the drug product.

RESIDUAL SOLVENTS

General Comments. Similar to the aforementioned comments about the "Chemical Purity" section, each of the tests and testing limits described in this section is applicable only if residual solvent is present in the final preparation of ^{18}F-FDG injection. By the same token, the methods and limits for residual solvents listed below may be omitted if the listed substances are not in the ^{18}F-FDG injection preparation. However, if other residual solvents may remain in the final preparation of ^{18}F-FDG injection, their potential toxic, physiologic, or pharmacologic effects must be considered. Any residual solvent with a potential for toxicity must be within appropriate limits, and conformance with these limits is to be demonstrated by the use of one or more validated limit tests.

Acetonitrile, Dehydrated Alcohol, and Ether

USP. No more than 0.04% acetonitrile, 0.5% dehydrated alcohol, and 0.5% ether are found in ^{18}F-FDG injection. Testing is performed using a GC system with flame ionization detection.

CMC. No more than 0.04% acetonitrile, 0.5% dehydrated alcohol, and 0.5% ether are found in ^{18}F-FDG injection. Testing is performed using a GC system with flame ionization detection. The test must be completed before release of the drug product.

EP. The concentration of acetonitrile does not exceed 4.1 mg per V, V being the maximum recommended dose, in milliliters. ^{18}F-FDG injection may be released for use before completion of the test.

Comments. The intravenous LD_{50} values in rats for acetonitrile and dehydrated alcohol are 1,680 and 1,440 mg/kg, respectively (*19*,*20*), whereas there is no information on intravenous LD_{50} in rats for ether. The oral LD_{50} values in rats for acetonitrile, dehydrated alcohol, and ether are 2,460, 7,060, and 1,215 mg/kg, respectively (*19*–*21*). One may wonder why acetonitrile has the lowest acceptance threshold (i.e., 0.04%) of the 3 residual solvents, when dehydrated alcohol has a lower intravenous LD_{50} value and ether has the lowest oral LD_{50} (*19*–*21*). According to the "Guidance for Industry Q3C Impurities: Residual Solvents" issued by the FDA in 1997, residual solvents are grouped into 3 classes (i.e., classes 1, 2, and 3) (*22*). The classification of residual solvents involves a risk assessment not only of their potential toxicity to humans but also of any possible deleterious effects they may have on the environment (*22*).

Based on the "Q3C: Tables and List," acetonitrile is categorized as a class 2 solvent, whereas both dehydrated alcohol and ether are categorized as class 3 solvents. Class 1 comprises solvents known to be human carcinogens, strongly suspected to be human carcinogens, or hazardous to the environment. Their use must be avoided in the manufacture of drug substances, excipients, and drug products. Class 2 solvents have inherent toxicity, and their use in pharmaceutical products must be limited (*22*,*23*). Class 3 solvents are those with a lower potential for toxicity and thus pose a lower risk to human health (*22*,*23*). Therefore, the acceptance percentage limit for acetonitrile is lower than that of dehydrated alcohol or ether.

The EP covers only 1 individual solvent, acetonitrile, and does not mention the method (e.g., GC) to be used to determine acetonitrile content (*4*). The exclusion of the other solvents (i.e., dehydrated alcohol and ether) within the "Residual Solvents" section of the EP may be related to their lower toxic potential. Because the GC process takes only a few minutes, it is not clear why the EP allows the final product to be released for patient use before the com-

pletion of GC testing. In the EP, the limit for acetonitrile is stated to be 4.1 mg per V, where V is the maximum recommended dose, in milliliters, whereas the limit stated in both the USP and the CMC is based on the concentration of acetonitrile in an ^{18}F-FDG injection (i.e., 0.04% w/v or 0.4 mg/mL) (*1*,*3*,*4*). As already discussed, the acceptable limit of an impurity must be based on its mass in the maximum dose volume administered to a patient; the V must be defined as the maximum dose, in milliliters, at the expiration time; and the concentration of the standard solutions must be adjusted accordingly. Nevertheless, depending on the injected volume of the ^{18}F-FDG injection, the limit for acetonitrile may differ between the EP and the USP/CMC: If the injected volume is less than 10 mL, the USP/CMC limit is less than the EP limit; if the injected volume is 10 mL, the USP/CMC limit is the same as the EP limit; and if the injected volume is more than 10 mL, the USP/CMC limit is greater than the EP limit.

Similar to the validation needed for an HPLC system, it is also important to evaluate the suitability of a GC system to ensure that its resolution and reproducibility are adequate for the analysis of residual solvents (*7*,*8*). According to the USP, the resolution between the standard and test solutions must be no less than 1.0, and the relative SD for replicate injections should not be more than 5% (*1*).

Because the EP contains little information on the testing on residual solvents (i.e., no acceptance limits are specified for dehydrated alcohol and ether, and no specific directions are included for the GC method), the QA requirements described in the USP and CMC are adopted for the proposed test for the evaluation of residual solvents in ^{18}F-FDG injection.

Proposed Test. No more than 0.04% acetonitrile, 0.5% dehydrated alcohol, and 0.5% ether are found in ^{18}F-FDG injection. The test is performed using a GC system with flame ionization detection. The test must be completed before release of the drug product.

BACTERIAL ENDOTOXINS

USP. No more than 175/V USP endotoxin units (EU) per milliliter of ^{18}F-FDG injection, in which V is the maximum administered total dose, in milliliters, at the expiration time.

CMC. No more than 175/V USP EU per milliliter of ^{18}F-FDG injection, in which V is the maximum recommended total dose, in milliliters, at the expiration time. The testing schedule must be stated.

EP. No more than 175/V international units (IU) of endotoxin per milliliter, in which V is the maximum recommended administered total dose, in milliliters.

Comments. During revision, the USP removed the word *recommended* from the "Bacterial Endotoxins" section, possibly because the administered total dose of ^{18}F-FDG injection is usually adjusted according to the patient's body weight and age. Also, the recommended dose for ^{18}F-FDG injection varies between PET centers.

Because the maximum administered total volume of ^{18}F-FDG injection at expiration time may be equal to the total volume of the entire batch of ^{18}F-FDG production, it would seem appropriate to calculate the bacterial endotoxin limit (i.e., 175/V USP EU) using the total ^{18}F-FDG volume in the batch vial for the V value. Although this approach is simple in that it does not take into consideration the maximum administered dose, decay factor, or expiration time, the result is a bacterial endotoxin limit with the lowest value because the total volume of the entire batch of ^{18}F-FDG injection, rather than a partial volume, is used as the denominator for calculation of the acceptable bacterial endotoxin limit.

The word *recommended* must be removed from the CMC section for ^{18}F-FDG injection for the reason stated above (*3*). It is not clear why the schedule for bacterial endotoxin testing is not specified in the CMC section.

The EP lists the same endotoxin limit as does the USP and the CMC, in consideration of the fact that 1 USP EU is equal to 1 IU of endotoxin (*24*). The EP should delete the word *recommended* from the bacterial endotoxin section, like the CMC section for ^{18}F-FDG injection.

The commonly used gel-clot technique for the determination of bacterial endotoxin concentration requires a 60-min incubation. The 60-min bacterial endotoxin test (BET) is described in USP <85>, "Bacterial Endotoxins Test" (*24*), and is also recommended for pyrogenicity testing in the draft guidance of the FDA on CGMP for PET drug products (*25*). Because the remainder of the required QA testing for ^{18}F-FDG injection, with the exception of the sterility test, can be completed in approximately 20–30 min, delaying the release of the short-lived ^{18}F-FDG injection for an additional 30–40 min is not practical and is, in fact, wasteful. This may be the reason that the CMC does not specify a testing schedule and the EP permits the ^{18}F-FDG injection to be released before completion of the test.

USP <823>, "Radiopharmaceuticals for Positron Emission Tomography: Compounding," indicates that an in-process 20-min endotoxin limit test can be used to allow for the possibility of an early release of any parenteral PET drugs with a half-life of more than 20 min; however, the standard 60-min BET must be performed and completed (*26*). This 2-part BET test is a sensible approach with regard to ^{18}F-FDG injection, because all other required QA testing procedures (except the sterility test) are completed in 20–30 min. Nonetheless, USP general chapter <823> applies only to compounded PET drug products that are not commercially available; it would therefore seem that ^{18}F-FDG injection is not intended for inclusion on the drug compounding sanction list (*26*). Also, it is interesting to note that the 20-min BET is not mentioned in USP <85>, "Bacterial Endotoxins Test" (*24*,*26*). Cooper noted a proposed test scheme for the 20-min BET (*27*).

Proposed Test. No more than 175/V USP EU (175/V IU) per milliliter of ^{18}F-FDG injection, in which V is the maximum administered total dose, in milliliters, at the expiration time. An in-process 20-min BET must be performed

before release of the drug product, and a standard 60-min BET must also be completed.

STERILITY

USP. Meets the requirements under USP <71>, "Sterility Test" (*28*), except that ^{18}F-FDG injection may be distributed or dispensed before completion of the sterility test. The sterility test must be started within 24 h of final manufacture.

CMC. Sterile. The sterility test must be initiated within 24 h of preparation.

EP. Complies with the test for sterility prescribed in the EP (*29*). ^{18}F-FDG injection may be released for use before completion of the test.

Comments. The recently released FDA regulatory documents on the CGMP requirements for PET drug products (i.e., preliminary draft proposed rule and draft guidance) (*25*,*30*) stipulate that sterility testing must be started within 24 h after the completion of PET drug production (i.e., after sterile filtration). Although matching the requirements in the USP and CMC, the 24-h window for the initiation of sterility testing is not practical.

When production of PET drug products (e.g., ^{18}F-FDG injection) is completed on a Friday afternoon, PET laboratory personnel may be required to return to the PET center to start the required sterility test either Friday evening or Saturday. In addition, for highly concentrated ^{18}F-FDG samples, a 24-h period is insufficient to allow radioactivity in the samples to decay to what would be considered nonradioactive (or background) levels. Serious consequences may result for PET drug production facilities that, for instance, send their samples to external facilities for sterility testing, when those outside laboratories do not accept any test sample that is radioactive. Because more than 24 h may be required for the radioactivity of an ^{18}F-FDG injection sample to decay to a background or undetectable level, I normally allow my ^{18}F-FDG injection samples to decay for at least 48 h before forwarding them to a microbiology laboratory for the sterility test.

In contrast to the USP and the CMC, the EP sensibly states that ^{18}F-FDG injection may be released before completion of the test (*1*,*3*,*4*). There is no requirement that the test be initiated within 24 h of final manufacture.

Proposed Test. Meets the requirements stated under USP <71>, "Sterility Test" (*28*), except that ^{18}F-FDG injection may be distributed or dispensed before completion of the test for sterility. The sterility test must be started after an appropriate decay period after final manufacture.

OSMOLALITY

USP. Unlisted.

CMC. Isotonic (the range must be specified).

EP. Unlisted.

Comments. The USP requires that ^{18}F-FDG injection be a sterile aqueous solution; the term *isotonic* has been removed from the USP (*1*). Because ^{18}F-FDG injection consists mainly of physiologic saline, it must be isotonic and the osmolality test for ^{18}F-FDG injection is therefore not necessary.

The CMC requires that the osmolality of ^{18}F-FDG injection be validated and yet does not specify the frequency of validation (*3*).

Proposed Test. For the reasons stated above, the osmolality of ^{18}F-FDG injection does not need to be tested.

GLUCOSE

USP. Unlisted.

CMC. No more than _____ mg/V, in which V is the total volume of the batch of ^{18}F-FDG injection produced.

EP. Unlisted.

Comments. The CMC does not specify the limit of glucose content in ^{18}F-FDG injection. The calculation of glucose content is based on the amount of mannose triflate used. Glucose is a by-product of ^{18}F-FDG injection synthesis and is present in low concentration in the final product. The minute amount of glucose in a typical ^{18}F-FDG injected dose should not harm patients with diabetes mellitus. For patients without diabetes mellitus, the glucose would not be considered a harmful impurity. Therefore, one must question the need to regularly perform such a test.

Proposed Test. The limit of glucose content must be based on physiologic and pharmacologic necessity.

STABILIZER

USP. Unlisted.

CMC. If a stabilizer is added, a test for its assay must be included in the specifications.

EP. Unlisted.

Comments. A stabilizer may be added to the formulation of ^{18}F-FDG injection to reduce the radiolytic degradation of ^{18}F-FDG with a high specific concentration. If the added stabilizer may cause toxic, physiologic, or pharmacologic effects, it must be evaluated to ensure that it meets the acceptance limit.

Proposed Test. If a potentially toxic stabilizer is added, a method, acceptance limits, and schedule (i.e., test must be completed before release of drug product) for its assay must be established and validated.

MEMBRANE FILTER INTEGRITY

USP. Unlisted.

CMC. A limit must be specified for the filter being used. The test must be completed before release of the drug product.

EP. Unlisted.

Comments. The CMC suggests the use of bubble point measurement to test membrane filter integrity (*3*,*26*). Because the sterility test is completed retrospectively, the

membrane filter integrity test may be considered to indicate the microbiologic integrity of the product. Thus, it is important that this test be included in the QA procedures for ^{18}F-FDG injection.

Proposed Test. Specify a limit for the filter being used. The test must be completed before release of the drug product.

CONCLUSION

The inclusion of an official test method in the USP does not preclude the use of an alternative (*31*). However, before using an alternative, one must be able to show that it is equivalent to the method described in the current USP. In the event of a difference between methods or of a dispute or doubt, the USP method is considered the referee method and only its result is considered conclusive (*31*). The EP contains a similar policy on the use of an alternative QA test method (*32*). For each of 3 approved PET drugs (i.e., ammonia ^{13}N injection, fludeoxyglucose ^{18}F injection, and sodium fluoride ^{18}F injection), the CMC lists QA tests for which the end user may be able to revise the recommended acceptance criteria, testing procedure, or testing schedule to meet production capability and constraint (*3*). Obviously, any such changes will need to be approved by the FDA.

Nevertheless, the standard, or recommended, QA tests stated in the official sources (e.g., USP, CMC, and EP) must be accurate and practical so that the end user can easily and, more important, faithfully perform them to provide the best-quality PET drug products for clinical use (*1*,*3*,*4*). Additionally, the PET community and the general, worldwide, public would benefit from having a set of standardized and internationally recognized QA test requirements for PET drugs. Worldwide harmonization of QA standards for PET drug products not only would follow the current trend with regard to drug standards but also would undoubtedly further enhance the safety of PET drugs. It is hoped that this article will stimulate the international PET community to work closely together to develop a better set of QA test guidelines for PET drugs.

ACKNOWLEDGMENTS

I thank Mark S. Jacobson (Mayo PET Radiochemistry Facility, Mayo Clinic, Rochester, MN) for the intriguing and helpful discussion of several QA issues related to ^{18}F-FDG injection, and I thank Vicki S. Krage (Nuclear Medicine, Department of Radiology, Mayo Clinic, Rochester, MN) for her kind assistance with the proofing and submission of the manuscript.

REFERENCES

1. Fludeoxyglucose F 18 injection. In: *The United States Pharmacopeia*, 25th ed., and *The National Formulary*, 20th ed. Rockville, MD: United States Pharmacopeial Convention, Inc.; 2002:752–753.
2. Positron emission tomography. In: *Food and Drug Administration Modernization Act of 1997.* Pub L No. 105-115, §121.
3. Fludeoxyglucose F 18 injection CMC section. In: *Sample Formats: Application to Manufacture Ammonia N 13 Injection, Fluorodeoxyglucose F 18 Injection (FDG F 18), and Sodium Fluoride F 18 Injection—Chemistry, Manufacturing, and Controls Section*. Rockville, MD: Food and Drug Administration; 2000:24–26. Available at: http://www.fda.gov/cder/guidance/cmcsample.pdf. Accessed August 14, 2002.
4. Fludeoxyglucose (^{18}F) injection. In: *European Pharmacopeia.* 4th ed. Strasbourg, France: European Directorate for the Quality of the Medicines; 2002:2316–2319.
5. Radiopharmaceutical preparation. In: *European Pharmacopeia.* 4th ed. Strasbourg, France: European Directorate for the Quality of the Medicines; 2002: 1361–1368.
6. Briner WH. USP monographs and tests of radiopharmaceutical purity [letter]. *Am J Health Syst Pharm.* 1995;52:1817–1818.
7. Chromatography (general chapter 621). In: *The United States Pharmacopeia*, 25th ed., and *The National Formulary*, 20th ed. Rockville, MD: United States Pharmacopeial Convention, Inc.; 2002:1982–1995.
8. *Facilities and Equipment Guidance: PET Drug Products—Current Good Manufacturing Practice (CGMP).* Rockville, MD: Food and Drug Administration; 2002:7–14.
9. Alexoff DL, Casati R, Fowler JS, et al. Ion chromatographic analysis of high specific activity ^{18}FDG preparations and detection of the chemical impurity 2-deoxy-2-chloro-D-glucose. *Int J Rad Appl Instrum [A].* 1992;43:1313–1322.
10. Füchtner F, Steinbach J, Mäding P, Johannsen B. Basic hydrolysis of 2-[^{18}F]fluoro-1,3,4,6-tetra-*O*-acetyl-D-glucose in the preparation of 2-[^{18}F]fluoro-2-deoxy-D-glucose. *Appl Radiat Isot.* 1996;47:61–66.
11. Meyer G-J, Matzke KHY, Hamacher K, et al. The stability of 2-[^{18}F]fluoro-2-deoxy-D-glucose towards epimerization under alkaline conditions. *Appl Radiat Isot.* 1999;51:37–41.
12. Hamacher K, Coenen HH, Stöcklin G. Efficient stereospecific synthesis of no-carrier-added 2-[^{18}F]fluoro-2-deoxy-D-glucose using aminopolyether supported nucleophilic substitution. *J Nucl Med.* 1986;27:235–238.
13. pH. In: *The United States Pharmacopeia*, 25th ed., and *The National Formulary*, 20th ed. Rockville, MD: United States Pharmacopeial Convention, Inc.; 2002: 2052–2053.
14. pH/px (test papers & solutions). In: *Fisher Catalog 2000/01*. Pittsburgh, PA: Fisher Scientific; 2000:1283.
15. Chaly T, Dahl JR. Thin layer chromatographic detection of Kryptofix 2.2.2. in the routine synthesis of [^{18}F]2-fluoro-2-deoxy-D-glucose. *Nucl Med Biol.* 1989;16: 385–387.
16. Mock BH, Winkle W, Vavrek MT. A color-spot test of the detection of Kryptofix 2.2.2. in the routine synthesis of [^{18}F]FDG preparation. *Nucl Med Biol.* 1997;24: 193–195.
17. Ferrieri RA, Schlyer DJ, Alexoff DL, Fowler JS, Wolf AP. Direct analysis of Kryptofix 2.2.2. in ^{18}FDG by gas chromatography using a nitrogen-selective detector. *Nucl Med Biol.* 1993;20:367–369.
18. 4,7,13,16,21,24-Hexaoxa-1,10-diazobicyclo-(8,8,8)hexacosane (Kryptofix 222) [material safety data sheet]. St. Louis, MO: Sigma-Aldrich; August 3, 2000.
19. Acetonitrile [material safety data sheet]. Oxford, U.K.: University of Oxford. Available at: http://www.physchem.ox.ac.uk/MSDS/AC/acetonitrile.html. Accessed August 14, 2002.
20. Anhydrous alcohol (reagent grade) [material safety data sheet]. Oxford, U.K.: University of Oxford. Available at: http://www.physchem.ox.ac.uk/MSDS/AL/alcohol,_anhydrous,_reagent. Accessed August 14, 2002.
21. Diethyl ether [material safety data sheet]. Oxford, U.K.: University of Oxford. Available at: http://www.physchem.ox.ac.uk/MSDS/DI/diethyl_ether.html. Accessed August 14, 2002.
22. Classification of residual solvents by risk assessment. In: *Guidance for Industry: Q3C Impurities—Residual Solvents.* Rockville, MD: Food and Drug Administration; 1997:3. Available at: http://www.fda.gov/cder/guidance/Q3Cfnl.pdf. Accessed August 14, 2002.
23. *Guidance for Industry: Q3C—Tables and List.* Rockville, MD: Food and Drug Administration; 1997. Available at: http://www.fda.gov/cder/guidance/Q3Ct&l.pdf. Accessed August 14, 2002.
24. Bacterial endotoxins test (general chapter 85). In: *The United States Pharmacopeia*, 25th ed., and *The National Formulary*, 20th ed. Rockville, MD: United States Pharmacopeial Convention, Inc.; 2002:1889–1893.
25. Finished drug product controls and acceptance criteria. In: *Guidance: PET Drug Products—Current Good Manufacturing Practice (CGMP).* Rockville, MD: Food and Drug Administration; 2002:27–28.
26. Radiopharmaceuticals for positron emission tomography: compounding (general chapter 823). In: *The United States Pharmacopeia*, 25th ed., and *The National Formulary*, 20th ed. Rockville, MD: United States Pharmacopeial Convention, Inc.; 2002:2068–2071.

27. Cooper JF. USP revision for radiopharmaceuticals for positron emission tomography (PET) takes effect June 2001. *LAL Times.* June 2001;8:1–2.
28. Sterility tests. In: *The United States Pharmacopeia*, 25th ed., and *The National Formulary*, 20th ed. Rockville, MD: United States Pharmacopeial Convention, Inc.; 2002:1878–1883.
29. Monographs on radiopharmaceutical preparations. In: *European Pharmacopeia.* 4th ed. Strasbourg, France: European Directorate for the Quality of the Medicines; 2002:2309–2355.
30. *Current Good Manufacturing Practice for Positron Emission Tomography Drugs: Preliminary Draft Proposed Rule.* Rockville, MD: Food and Drug Administration; 2002:68.
31. General notices and requirements. In: *The United States Pharmacopeia*, 25th ed., and *The National Formulary*, 20th ed. Rockville, MD: United States Pharmacopeial Convention, Inc.; 2002:1–11.
32. General notices. In: *European Pharmacopeia*, 4th ed. Strasbourg, France: European Directorate for the Quality of the Medicines; 2002;1–12.

Erratum

The article "Labeling of Cerebral Amyloid β Deposits In Vivo Using Intranasal Basic Fibroblast Growth Factor and Serum Amyloid P Component in Mice," by Shi et al. (*J Nucl Med.* 2002;43:1044–1051), contains an error in the reported concentration of injected ^{125}I-bFGF. The third sentence in column 2 of page 1045 should read "For mice in the first 2 groups, 6 drops (1.5 μL each) of ^{125}I-bFGF (1.85 MBq/mL per 10 g of body weight) were injected by a tapered-end plastic tip to each nostril, 1 drop every 5 min with the mouse supine." The authors regret the error.