Guidance

PET Drug Products – Current Good Manufacturing Practice (CGMP)

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Brenda Uratani, 301-827-8941.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
September 2005
Compliance

Guidance

PET Drug Products – Current Good Manufacturing Practice (CGMP)

Additional copies are available from:

Office of Training and Communications
Division of Communications Management
Drug Information Branch, HFD-210
5600 Fishers Lane
Rockville, MD 20857
(Tel) 301-827-4573
(Internet) http://www.fda.gov/cder/guidance/index.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
September 2005
Compliance

TABLE OF CONTENTS

Guidance[1]

PET Drug Products – Current Good Manufacturing Practice (CGMP)

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

If you plan to submit comments on this draft guidance, to expedite FDA review of your comments, please:

- *Clearly explain each issue/concern and, when appropriate, include a proposed revision and the rationale/justification for the proposed change.*
- *Identify specific comments by line number(s); use the PDF version of the document, whenever possible.*

I. INTRODUCTION

This draft guidance is intended to help PET drug producers better understand FDA's thinking concerning compliance with the proposed CGMP regulations. The guidance addresses resources, procedures, and documentation for all PET drug production facilities, academic and commercial. In some cases, the guidance provides practical examples of methods or procedures that PET production facilities could use to comply with the proposed CGMP requirements. In developing this draft guidance, FDA has taken into consideration relevant issues, concerns, and questions raised at the public meetings held with professional associations, producers of PET drug products, and other interested parties. A first draft version of this guidance was issued in April 2002 in conjunction with revised preliminary draft proposed regulations.

FDA's guidance documents, including this guidance, should not be viewed as establishing legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

[1] This guidance has been prepared by the PET Steering Committee in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA).

II. BACKGROUND

Section 121(c)(1)(A) of the Food and Drug Administration Modernization Act of 1997 (the Modernization Act) directed the Food and Drug Administration (FDA) to establish current good manufacturing practice (CGMP) requirements for positron emission tomography (PET) drugs. Concurrently with the issuance of this draft guidance, FDA is proposing such requirements under 21 CFR Part 212. In 1999, FDA published a preliminary draft of the proposed PET CGMP regulations.[2] The FDA received comments on the preliminary draft proposed regulations at a public meeting on the subject on September 28, 1999. The FDA made changes in the working draft in response to the public comments. In 2002, a revised preliminary draft of the CGMP regulations[3] was published in conjunction with a first draft of this guidance.[4] The FDA received comments on the preliminary proposed rule and the draft guidance at a public meeting on May 21, 2002, and in writing after the meeting and has taken all comments into consideration in revising the proposed rule and this draft of the guidance. This second version of the draft guidance provides more details for discussion purposes on acceptable approaches to complying with the proposed regulations should they be published in final form.

As directed by Congress in the Modernization Act, to help in developing the proposed regulation and this draft guidance, we closely examined the operations of many PET drug producers, including not-for-profit institutions and commercial manufacturers. Since the Modernization Act became law, significant changes have occurred in PET drug production in the United States. The number of PET production facilities has increased, as has the number of facilities where PET scans are performed. The business of PET drug production has changed as well. Historically, PET drug products were produced by academicians and researchers at PET production facilities located in universities and similar not-for-profit institutions. An academically oriented PET production facility usually produces small amounts (a few doses per day) of a few PET drug products for on-site patient use and a larger variety of PET drug products for clinical investigation and academic research.

An increasing number of PET production facilities are now operated by for-profit corporate entities that contract with academic and medical institutions (many of which have not-for-profit status) to manage the production of PET drugs at those institutions. Most of these PET drug products are administered on site, although often there is some distribution to other local or regional hospitals. In addition, a growing number of independent PET production facilities are not affiliated with any university or hospital. These for-profit, often contractually managed, and independently operated PET production facilities distribute PET drug products to significantly greater numbers of patients, sometimes hundreds of miles from the production site.

---

[2] See FDA's Web site at www.fda.gov/cder/fdama/212draft.htm and notice of availability, 64 FR 51274; September 22, 1999.

[3] See FDA's Web site at www.fda.gov/cder/fdama/cgmpdpr.pdf and notice of availability, 67 FR 15344; April 1, 2002.

[4] See FDA's Web site at www.fda.gov/guidance/4259dft.htm and notice of availability, 67 FR 15404; April 1, 2002.

Our review of PET drug production has lead to the conclusion that a PET drug producer's status as either a not-for-profit or for-profit entity has little bearing on the quality of PET drugs that it produces and distributes for administration to patients, or on the methods, facilities, and controls that a PET production facility needs to ensure product quality. Instead, production and CGMP differences among PET drug producers are primarily a function of the size, scope, and complexity of their production operations. We have also found that implementing certain production standards and controls can ensure the production of quality PET drugs, regardless of differences among the various PET production facilities. The Agency believes that the welfare of a patient undergoing a PET scan should not depend on where a particular PET drug was manufactured.

The proposed regulations on CGMP requirements contain what we believe are the minimum standards for quality production of PET drugs at all types of PET production facilities. We have designed the CGMP regulations to be sufficiently flexible to accommodate not-for-profit, academically oriented institutions as well as commercial producers.

The proposed regulations also incorporate principles from the United States Pharmacopeia (USP) general chapter on PET drug compounding. The USP contains standards that are of significant regulatory importance for PET drugs. Currently, under section 501(a)(2)(C) of the Federal Food, Drug, and Cosmetic Act (the Act), a compounded PET drug is adulterated unless it is produced in compliance with USP compounding standards and official monographs for PET drugs. Section 121(b) of the Modernization Act added this provision as a safety net during the time it takes the Agency to develop the final regulations. Under section 121(b) however, section 501(a)(2)(C) of the Act will expire 2 years after the date on which we establish approval procedures and CGMP requirements for PET drugs. At that time, compliance with the final version of the regulation will be required. Nevertheless, the USP general chapter on PET drug compounding largely reflects the consensus views of the PET community and FDA on how to properly produce PET drug products. Consequently, we believe it is appropriate to incorporate many of the principles and concepts in the USP general chapter into the proposed CGMP requirements.

Proposed § 212.5(b) specifies the CGMP requirements for investigational, research, and approved PET drugs. Proposed § 212.5(b)(1) states that the regulations in part 212 apply to all PET drug products for human use, other than research and investigational PET drug products. We believe that it is appropriate to have less detailed CGMP requirements for investigational and research PET drugs to allow more flexibility during the development of these drugs. We also recognize that many investigational PET drugs may not have commercial potential. Therefore, proposed § 212.5(b)(2) states that the regulations in part 212 do not apply to investigational PET drugs for human use produced under an investigational new drug application in accordance with part 312 and research PET drugs that are produced with the approval of a Radioactive Drug Research Committee (RDRC) in accordance with § 361.1.

Instead, proposed § 212.5(b)(2) states that, for investigational and research PET drugs, the requirement under the Act to follow CGMP is met by producing drugs in accordance with Chapter <823> of the 26th edition of the USP (2003). Chapter <823> sets forth requirements for

PET drug production, including control of components, materials, and supplies; verification of procedures; stability testing and expiration dating; quality control; and sterilization and sterility assurance. Because most PET drug producers are very familiar with the requirements in Chapter <823>, adopting the Chapter <823> provisions as the CGMP requirements for investigational and research PET drugs should greatly facilitate producers' compliance with those requirements. Although the provisions in Chapter <823>, including those on documentation, are generally less specific and explicit than the requirements in proposed part 212, we believe that they are adequate to ensure that investigational and research PET drugs are produced safely under appropriate conditions, consistent with section 501(a)(2)(B) of the Act.

Although we propose that USP Chapter <823>, rather than part 212, would constitute the minimum CGMP requirements for investigational and research PET drugs, FDA would retain the authority to inspect facilities where investigational and research PET drugs are produced to verify compliance with Chapter <823>. However, as with inspection of investigational studies of non-PET drugs, we generally would conduct inspections of facilities that produce investigational or research PET drugs only on a for-cause basis (i.e., when we become aware of a potential safety concern related to the production of an investigational or research drug).

PET drugs, other than investigational and research PET drugs, would have to meet the requirements of proposed part 212. PET drug products that would have to be marketed under an approved new drug application (NDA) or an approved abbreviated new drug application (ANDA) would have to be produced in accordance with proposed part 212.

III. PET DRUGS AND CGMP REQUIREMENTS

A. What is a PET Drug?

PET is a medical imaging modality that requires the use of a unique type of radiopharmaceutical drug. A PET drug exhibits spontaneous disintegration of unstable nuclei by the emission of positrons (β^+). PET drugs are used to provide dual photon positron emission tomographic images. The radionuclide is generally produced by a particle accelerator (e.g., a cyclotron) and has a short half life. Currently, a batch, or lot, of a PET drug typically consists of one multiple-dose vial containing the PET drug product in a sterile solution. A sample from the vial, which is representative of all doses to be administered, is tested to verify that the batch or the lot conforms to all established specifications.

A PET drug product is typically administered to patients within a few minutes to a few hours following preparation. Because of the short half life of the radionuclide and the mode of production, PET drug products have unique storage, shipping, and handling concerns. Under Section 121 of the Modernization Act, PET producers must comply with the standards in the USP General Chapter <823> *Radiopharmaceuticals for Positron Emission Tomography-Compounding*, until FDA establishes approval procedures and CGMPs for PET drug products.

B. What is CGMP?

Current good manufacturing practice (CGMP) is a minimum standard that ensures that a drug meets the requirements of safety and has the identity strength, quality, and purity characteristics it is represented to possess. The Agency is proposing CGMP regulations that would require manufacturers of PET drugs to follow certain CGMP requirements. CGMP is demonstrated through written documentation of procedures and practices. The documents and practices may be similar or identical to documents and practices requested by other oversight bodies (e.g., Nuclear Regulatory Commission and state and local agencies). Documents produced for others, where appropriate, can be used to provide the documentation of compliance with CGMP requirements. However, because of institutional, local, or state differences, some of these documents may not have sufficient overlap to address the issues in this guidance. Therefore, to ensure uniformity for all patients and human subjects, where overlap does not exist, we recommend that PET producers develop supplemental documentation.

C. Distinguishing Between PET Drug Production and the Practice of Pharmacy

FDA regulates the production of PET drug products. Section 121 of the Modernization Act directs FDA to establish appropriate approval procedures for PET drugs pursuant to section 505 of the Act as well as appropriate CGMP requirements. In the course of developing these approval procedures and CGMP requirements, a question has been raised concerning how to distinguish PET drug production from the practice of pharmacy (regulation of which FDA has traditionally deferred to State and local authorities).

FDA has determined that the *production* of a PET drug product includes all operations to the point of final release of a finished dosage form, and these activities would be subject to CGMP. A PET drug product may be released to a hospital, institution, imaging facility, nuclear pharmacy (e.g., pharmacy bulk packages for use in accordance to USP <1> *Injections*), or other entity or part of an entity. After a finally released PET drug product is received by the receiving facility, FDA generally regards subsequent dispensing of a patient-specific dose and use of the drug product to be part of the practice of medicine and pharmacy. FDA generally will defer to State and local authorities concerning regulation of these activities. In general, a routine FDA inspection to ensure compliance with CGMP would focus on activities up to and including the point of final release of a PET drug product.

In the following sections, the draft guidance introduces each section by identifying the relevant requirements from the proposed regulations. The section then provides more detailed current thinking. Certain CGMP requirements in the proposed regulations are self-explanatory and have not been further clarified in this guidance.

IV. PERSONNEL RESOURCES

A. Regulatory Requirements

Proposed 21 CFR 212.10 would require a PET production facility to have a sufficient number of personnel with the necessary education, background, training, and experience to enable them to

perform their assigned functions correctly. Each center also would have to provide adequate resources, including equipment and facilities, to enable their personnel to perform their functions.

The following section of the guidance addresses personnel. Guidance on resources (facilities and equipment) is provided in Section VI.

B. Organization and Staffing

We recommend that staffing levels correspond to the size and complexity of the operation of the PET production facility and enable a PET production facility to satisfactorily complete all intended tasks in a timely manner before administration of a finished PET drug to humans. We recommend that the responsibilities and assigned duties of all staff be clearly identified in written policies.

For a PET production facility that typically produces one or two batches of a product daily, it may be adequate to employ one or two persons to accomplish all production and quality control functions. We recommend the PET facility demonstrate that the production and quality control functions can be consistently accomplished in a timely and appropriate manner before administration of a drug to humans. One individual can be designated to perform the production as well as quality control functions, provided he or she is highly qualified in the performance of all such functions (i.e., has a degree, documented training, and significant experience in the technical area).

Under current CGMP regulations in 21 CFR Part 211, FDA normally requires second-person checks at various stages of production as well as test verification. In a PET production facility with only one person assigned to perform production and quality control tasks, it is recommended that that person recheck his or her own work. Self-checks involve the confirmation of the operator's own action and would be documented. Examples of self-check activities include reviewing batch records (e.g., review the batch record to ensure that all finished-product test results are within the acceptance criteria) before release of the drug product for distribution and verifying calculations in analytical tests.

At a PET production facility that produces multiple PET drugs, we recommend the staffing level be adequate to perform all quality assurance functions and to prevent mix-ups and cross contamination.

C. Personnel Qualifications

As mentioned above, each person performing an activity or a function in the production and quality control of a PET drug product would have to have the appropriate education, training, and experience related to that function and should be trained in CGMP relevant to their assigned tasks. We recommend that PET production facilities have adequate ongoing programs or plans in place for training employees in new procedures and operations and in the areas where deficiencies have occurred.

We recommend PET production facilities maintain an updated file (e.g., curriculum vitae, copies of degree certificates, certificate of training) for each employee.

V. QUALITY ASSURANCE

A. Regulatory Requirements

Proposed 21 CFR 212.20 would require PET production facilities to have a quality assurance function. Under the proposed regulations, the following activities are defined as the responsibilities of the quality assurance function:

- Oversee production operations to ensure that PET drug products have adequately defined identity, strength, quality, and purity
- Examine and approve or reject components, containers, closures, in-process materials, packaging materials, and labeling used in the production of PET drug products to ensure that all these meet their current specifications
- Examine any procedure affecting production, testing, and specifications
- Review production records for accuracy and completeness
- Ensure that all errors are investigated and corrective action is taken

B. The Activity and Responsibility of the Quality Assurance Function

The quality assurance function in a PET production facility typically consists of execution and oversight activities.

We recommend that the execution of quality assurance functions include the following:

- Examine and evaluate each lot of incoming material before use to ensure that the material meets its established specifications
- Review the production batch records and laboratory control records for accuracy, completeness, and conformance to established specifications before authorizing the final release or rejection of a batch or lot PET drug product

We recommend that the oversight of quality assurance functions include the following:

- Approve procedures, specifications, process, and methods
- Ensure that personnel are properly trained and qualified, as appropriate
- Ensure that PET drugs have adequately defined identity, strength, quality and purity
- Investigate errors and ensure that appropriate corrective action is taken to prevent their recurrence
- Conduct periodic audits to monitor compliance with established procedures and practices

For PET production facilities currently producing one or two PET drugs, employees located at the facility can perform both the daily execution and oversight functions.

On the other hand, a commercial PET firm managing multiple production facilities may choose to have an entity located outside the PET production facility help to achieve the objective of manufacturing oversight and more efficient management. For example, a corporate quality assurance/quality control department, or consultants, can provide oversight.

VI. FACILITIES AND EQUIPMENT

A. Regulatory Requirements

Proposed 21 CFR 212.30(a) would require that a PET production facility have adequate facilities to ensure the orderly handling of materials and equipment, the prevention of mix-ups, and the prevention of contamination of equipment or product by substances, personnel, or environmental conditions.

Proposed 21 CFR 212.30(b) and (c) would require that all equipment that would reasonably be expected to adversely affect the strength, quality, or purity of a PET drug, or give erroneous or invalid test results when improperly used or maintained, is clean, suitable for its intended purposes, properly installed, maintained, and capable of repeatedly producing valid results. Equipment would have to be constructed so that surfaces that contact components, in-process materials, or drug products are not reactive, additive, or absorptive so as to alter the quality of the PET drug product.

B. Facilities

1. General

The design of the PET drug production facility should promote orderly operations during the production process and protect the product from contamination originating from personnel and surrounding areas. To achieve this, a facility should contain adequate work areas suitable for the intended tasks (e.g., area for analytical testing, aseptic manipulation, chemical production, radiochemical production, and component storage) and to allow completion of all production-related tasks in an orderly manner. Potential sources of contamination include particulate matter and chemical and microbiological materials.

Phases of production with the potential for microbiological contamination should be performed under environmental conditions that minimize the possibility of such contamination (e.g., in a laminar airflow workbench (LAFW), or barrier isolator system).

The placement of equipment and materials should be carefully evaluated to promote efficient operation and eliminate errors, mix-ups, and cross-contamination. All

equipment used in production (e.g., particle accelerator, synthesis units, or other specialized equipment) should be appropriately located and housed (e.g., with shielding) so that all the work areas during the normal course of production are easily accessible.

We recommend that related work areas be organized and proximally located so as to promote efficient operation and eliminate the potential for errors in the production and control operations. Access to work areas, production and testing equipment, components, containers and closures, and the PET drug products, should be restricted to authorized personnel.

In most PET production facilities, the same area or room can be used for multiple purposes. For example, the production (e.g., radiochemical synthesis), laboratory operation (e.g., release testing), and storage of approved components, including containers and closures, can be located in the same room. Components that are approved for use as well as those that are under quarantine can be stored in the same area or on a different shelf in a cabinet, provided each lot is properly labeled as to its status and contents and organized in a manner that avoids mix-up or unintended use. Rejected components, containers and closures, and other materials should be kept separate from quarantined or approved materials.

As the complexity in a PET production facility increases (production of multiple PET drug products), it is important to develop the appropriate level of control required to prevent mix-ups and contamination). Separate and well-defined areas or rooms may be warranted for each independent function of the operation, such as production, testing, and storage of components. It is also important to consider what impact a greater number of personnel and activities could have on the aseptic processing portion of the process.

2. Aseptic Processing Area

An aseptic work area should be suitable for the assembly of the aseptic components required for the preparation of a sterile PET drug product. We recommend that air quality in the aseptic processing area be controlled to limit the presence of microorganisms and particulate matter. Critical activities in the production and testing of a PET drug product that expose the PET drug product or the sterile surface of the container/closure system to the environment should be conducted within an aseptic workstation (e.g., a LAFW or barrier isolator). Examples of such activities include the aseptic assembly of sterile components (syringe, needle, filter and vial) for sterile filtration of the PET drug product, and sterility testing of the finished PET drug product. We recommend that the following precautions be taken to help maintain the appropriate air quality of the aseptic workstation:

- The aseptic workstation is sanitized before each operation.

- Items within a laminar airflow aseptic workstation are kept to a minimum and not interrupt the airflow.

- Operators wear clean lab coats and sanitized gloves when conducting an aseptic manipulation within the aseptic workstation.

- Gloved hands are frequently sanitized or changed when working in the aseptic workstation. Gloves are examined for damage (tears or holes) and replaced if they are compromised.

- The surface of nonsterile items (e.g., test tube rack, and the overwrap for sterile syringes, and filters) are sanitized and wiped with an appropriate disinfectant (e.g., sterile 70 percent isopropyl alcohol) before being placed in the aseptic workstation.

We recommend that conditions in the room where aseptic manipulations are conducted not present a challenge to the operating capability of the aseptic workstation. For example, the room should not be carpeted nor have overhanging pipes or hanging light fixtures. All areas of the production and processing room should be easily accessible for cleaning. Surfaces of the walls, floors, and ceilings in the aseptic work areas should be easily cleaned. Cleaning should be performed frequently to ensure consistent control of the environmental quality. In addition, the aseptic processing area (e.g., LAFW) should be situated in the section of the room with the lowest traffic and lowest activity. Cartons and boxes should not be stored or opened in the production area to minimize ingress of dust and particulate into the aseptic work area.

C. Equipment

1. Production Equipment

Equipment used in the production, processing, or packaging of a PET drug product would have to be appropriate for the performance of its intended function and not contaminate the product. We recommend that each piece of equipment be suitably located to facilitate its use, cleaning, and maintenance. We also recommend that each PET production facility establish and follow written procedures that address the following issues, where applicable:

- Assignment of responsibility and frequency for cleaning and maintenance of equipment

- Description of cleaning and maintenance procedures in sufficient detail to include disassembly and reassembly of equipment

- Protection of clean equipment from contamination prior to use

- Inspection of equipment and calibration, if indicated, prior to use

We recommend that each PET production facility select suitable cleaning agents and cleaning techniques and ensure that their cleaning operations not contaminate the drug product.

We recommend that newly installed equipment be qualified before first use to verify that it was installed correctly and is capable of operating as intended. Normally, the equipment vendor verifies that the equipment is installed correctly (installation qualification (IQ)) and operates according to specifications (operational qualification (OQ)). Before the equipment is used for production, personnel in the PET production facility should verify that the equipment, when operated under actual production parameters or selected method, produces consistent results within established specifications (performance qualification (PQ)).

We recommend developing a preventive maintenance schedule with sufficient frequency to ensure the correct performance of the equipment. Where needed, calibration should be performed prior to the use of the equipment for the intended task. We recommend facilities follow calibration checks recommended by equipment vendors unless the PET production facility has determined that more frequent calibrations are appropriate. Major repairs or upgrades in equipment may warrant requalification. We recommend not using malfunctioning or incorrectly operating equipment until repairs or corrective action have been made and the equipment has been found to operate correctly. All qualification, calibration, and maintenance activities should be properly documented, including the date of such performance and who performed them.

FDA recognizes that, after they become subject to the requirements of the final CGMP regulations, a number of PET production facilities may continue to use existing equipment. If they do, PET production facilities would have to make sure that the existing equipment is working properly and is being maintained and calibrated according to written procedures.

We recommend that PET production facilities establish procedures to check the correct functioning of the equipment that is developed in-house. Representative equipment is discussed below to illustrate how it might be controlled in a PET production facility.

a. Automated radiochemical synthesis apparatus

The apparatus enables the PET production facility to carry out the production process reliably and reproducibly. The provisions contained in the USP General Chapter <1015> *Automated Radiochemical Synthesis Apparatus* can help ensure proper functioning of a synthesis apparatus.

Prior to the production of a PET drug product each day, we recommend that the operator should conduct a performance check to ensure the following:

- The synthesis apparatus has been cleaned/flushed according to the established procedures.

- All appropriate tubing, reaction vessels, purification columns or cartridges, and other materials have been replaced and connected as required.

- The monitoring and or recording devices (e.g., temperature, pressure, flow rate) are functioning properly.

- When the process is under microprocessor control, the operator ensures that the system is functioning and recording correctly and that the correct program and operational parameters are used.

b. Aseptic Workstation

The aseptic workstation should provide an appropriate environment for aseptic procedures. Examples of workstations include a laminar air flow workbench (LAFW) or barrier isolator system. We recommend that an integrity test be conducted at installation (including after each change of the high-efficiency particulate air (HEPA) filter) to ensure proper performance. We recommend that certification (integrity testing of the HEPA filter) of the aseptic workstation be performed when the unit is initially installed and at least every 6 months thereafter to ensure the desired air quality. More frequent testing may be appropriate if air quality is found to be unacceptable, for example, as part of an investigation into a finding of sterility failure in a PET drug, or if leakage or decrease in optimal airflow is found.

We recommend that a qualified operator change the prefilters in the aseptic workstation periodically in accordance with written procedures and preventive maintenance schedules. Some laminar flow hoods are equipped with easily readable static pressure gauges that indicate when the pressure builds up behind the filter because of the clogging of the filter. We recommend that the filter be changed when clogging is detected.

We recommend laminar airflow velocities be monitored periodically at the work surface as well as at the HEPA filter face to ensure adequate uniformity of flow throughout the critical area. We recommend that operators be trained on the importance of minimizing objects and equipment within the critical area so laminar airflow is not disrupted. We recommend that microbiological monitoring (e.g., using settle plate) in the LAFW be conducted during sterility testing and critical aseptic manipulation.

c. Electronic or analytical weight balance

We recommend that written procedures, if not already available, be developed, describing the proper use of the balance, assessment of accuracy, and a schedule for calibration. We recommend that performance be checked by weighing two or more standard weights on each day of use. We recommend that the calibrated

weights used for assessing daily performance bracket the range of the weights being measured. We also recommend that the balance be fully calibrated periodically, or upon failure to meet daily performance checks (see USP <41> *Weights and Balances*).

d. Dry-heat ovens

If glassware and heat-stable materials are depyrogenated and sterilized on-site, we recommend that the PET production facility demonstrate and document that the depyrogenation cycle will achieve at least a 3-log reduction of an endotoxin challenge, as measured by a bacterial endotoxins test. A suitable challenge study usually involves random placement of endotoxin indicators in a representative oven load of materials. Suitable endotoxin indicators include glass vials that contain 1,000 to 10,000 Endotoxin Units.

e. High performance liquid chromatograph (HPLC)

When an HPLC is used for purification of a PET drug, we recommend the operator ensure that the system is working properly and there is no bleeding of unintended materials (e.g., column material) into the mobile phase.

f. Temperature recording device

We recommend that the temperature and humidity (where appropriate) of the dry heat oven, refrigerator, freezer, and incubator be recorded on each workday when in use. Automated recording devices are recommended for ease of documentation and for recording any deviations.

2. Quality Control Equipment

We recommend that PET production facility have the appropriate equipment to adequately perform each quality control function that it intends to perform. Representative quality control equipment can include:

a. Gas chromatograph (GC)

Prior to each day of its use, the analyst should make sure that the GC system is functioning correctly by conducting system suitability testing. At least one injection of the standard preparation (reference standard or internal standard) should be done before the injection of test samples (see USP General Chapter <621> *Chromatography*).

b. High performance liquid chromatograph (HPLC)

We recommend that the HPLC system have detectors suitable for the intended purpose and be of sufficient sensitivity. Prior to each day of its use, the analyst

should make sure that the HPLC system is functioning correctly by conducting system suitability testing (see USP General Chapter <621> *Chromatography* and FDA reviewer guidance, *Reviewer Guidance Validation of Chromatographic Methods* (November 1994). At least one injection of the standard preparation (reference standard or internal standard) should be done before the injection of test samples.

c. Dose calibrator

We recommend a dose calibrator be used to measure the radioactivity of PET drug products. Accuracy and linearity should be assessed at installation and at appropriate intervals thereafter. The instrument should be calibrated in accordance with nationally recognized standards or the manufacturer's instructions. System suitability testing should include a constancy check with a suitable high-energy radionuclide standard source.

d. Radiochromatogram scanner

We recommend that a radiochromatogram scanner (or equivalent equipment that provides a radiochromatogram) be used to measure radioactivity distribution in the developed thin layer chromatography plate (e.g., instant thin-layer chromatography (ITLC), paper or plate). The scanner should have sufficient sensitivity and spatial resolution for the intended discriminatory and quantitative objective. Manufacturer recommended checks and maintenance should be performed on the radiochromatogram scanner (see USP General Chapter <821> *Radioactivity*).

e. Multichannel analyzer (MCA)

A multichannel spectrometer coupled to a calibrated sodium iodide scintillation detector (or preferably with the higher resolution germanium lithium compensated, Ge (Li) detector) can be useful to determine radionuclidic purity and to identify the radionuclide. The overall system should have sufficient sensitivity and resolution for the intended purpose (see USP General Chapter <821> *Radioactivity*). Adequate calibration using National Institute of Standards and Technology (NIST) traceable standards and preventive maintenance should be performed at intervals specified in a written procedure and as recommended by the equipment manufacturer. More frequent intervals should be used if problems in the operation of the MCA are encountered.

VII. CONTROL OF COMPONENTS, CONTAINERS, AND CLOSURES

A. Regulatory Requirements

Proposed 21 CFR 212.40(a) and (b) would require PET production facilities to establish, maintain, and follow written procedures for the control of components, containers, and closures. There would have to be appropriate written specifications for components, containers, and closures.

Proposed 21 CFR 212.40(c) would establish the minimum standards for controlling components, containers, and closures from receipt to consumption.

Proposed 21 CFR 212.40(d) would require that components, containers, and closures be handled and stored in a manner that prevents contamination, mix-ups, and deterioration.

Proposed 21 CFR 212.40(e) would require that PET production facilities keep a record of each shipment of each lot of components, containers, and closures that they receive.

B. Control of Components, Containers, and Closures

The written procedures would have to specify how each material (components, containers, and closures) will be selected and controlled in PET production facilities. Procedures should cover the life cycle of a material, from time of receipt to ultimate consumption. The process for procurement and use of materials should include the following elements, where applicable:

1. Vendor Selection

We recommend only qualified vendors be used. A vendor is qualified when there is evidence to support its ability to supply a material that consistently meets all quality specifications. We also recommend that PET production facilities ask the vendor to report any major changes in the manufacture of an item. It is preferable to have more than one qualified vendor for a component. A vendor should be replaced if there is an indication that it is supplying unsatisfactory materials.

2. Receipt of materials

We recommend that each lot of material be checked upon receipt to determine that the order was filled correctly and arrived in good condition. Each lot should be logged in and assigned a new identification code number. The code number would be used in the disposition of that lot. Sufficient information should be documented to enable the PET production facility to have full traceability of each lot. We recommend that, before release for use, incoming materials be segregated and placed under quarantine and labeled as *Quarantined*. A lot can then be inspected, sampled, and tested, if applicable.

3. Acceptance, release, and storage of materials

Analytical results in the certificate of analysis (COA) for each lot of incoming material should be inspected against the PET production facility's current specification sheet to ensure that acceptance criteria are met. Where appropriate, certain components described below (see Acceptance Testing) can be tested to confirm their identity before they are accepted and released for use in the production of a PET drug product.

Materials that meet a PET production facility's specifications can be approved and released for use. Such release should be recorded and the examination and testing data maintained. It may be helpful to have a component logbook to record information such as receipt date, quantity of the shipment, supplier's name, lot number, expiration date, results of any testing performed, and person responsible for release.[5] Approved materials can be labeled *Approved* with an identifying code number, storage conditions, and expiration date. We recommend that materials be stored under the proper storage conditions and in an area designated for approved materials. If a lot is rejected, we recommend it be labeled *Rejected*, segregated, properly disposed of, and each of these actions be documented.

We recommend that items be stored under the conditions recommended by the vendor (e.g., temperature and humidity). Moisture sensitive materials should be stored in desiccated devices in sealed containers. There should be an expiration date for each item. We recommend that PET production facilities have a policy that guides the expiration dating of items, by category. Vendor assigned expiration dates could be used unless the in-house date is sooner.

4. Acceptance Testing

a. Reagents, solvents, gases, purification columns, and other auxiliary materials

We recommend that PET production facilities have procedures in place to ensure that only materials meeting applicable specifications from approved reliable sources are used. The COA and container label for each lot of each shipment of incoming materials should be examined to ensure that all specifications are met.

b. Components that yield an active pharmaceutical ingredient (API) and inactive ingredients

Under proposed § 212.40(c)(1)(i), for the production of PET drugs where finished-product testing ensures that the correct components have been used (e.g., production of F18 FDG) PET producers may rely on the certificate of analysis (COA) from the suppliers. Analytical results in the COA for each lot of component would have to be examined and compared against the PET production

[5] A sample format for record keeping of incoming components is available at *www.fda.gov/cder/regulatory/pet*.

facility's current specifications to ensure that acceptance criteria are met. We recommend that PET producers have scientific rationale and supporting data to justify why identity testing is not needed.

Under proposed § 212.40(c)(1)(ii), for the production of a PET drug where the finished-product testing does not ensure that the correct components have been used, identity testing would have to be performed. When specific identity tests exist, we recommend that they be used.

The inactive ingredients in PET drugs usually consist of a diluent, a stabilizer, and/or a preservative. Under proposed § 212.40(c)(1)(ii), if a product that is marketed as a finished drug product intended for intravenous administration is used as an inactive ingredient, it would not be necessary to perform a specific identity test for that ingredient. Proposed § 212.40(c)(1)(ii) also states that if an inactive ingredient (e.g., 0.9 percent sodium chloride solution) was prepared on site, an identity test on the components used to make the inactive ingredient would have to be performed before it was released for use.

c. Commercially available ready-to-use sterile, pyrogen-free, sealed container/closure systems for injections, syringes, transfer sets, and filters used in aseptic process

We recommend that PET production facilities use reliable sources for these items. Most PET production facilities use sterile and depyrogenated containers (sealed vials with stoppers and crimps) that are commercially available (510K product). Under proposed § 212.40(c)(2), a visual identification of each lot of containers and closures would have to be conducted. We recommend that a COA showing conformance with the established specifications be obtained before accepting a lot of the container/closure system. We recommend that the container/closure system be properly stored under appropriate environmental conditions (e.g., correct temperature, humidity, and sterility).

If the sterilization and depyrogenation of the container/closure are performed on site, we recommend that the efficacy of each process be demonstrated. We recommend that established procedures be shown to be reproducible and used in such cases.

5. Handling of components, containers, and closures

When a lot of material has met all acceptance criteria, the material can be labeled *Approved*. Under proposed § 212.40(d), approved materials would have to be handled and stored in a manner that prevents degradation or contamination. Unacceptable materials should be promptly rejected, identified, and segregated to prevent their use prior to appropriate disposal.

6. Records

Under proposed § 212.40(e), records would have to be kept for each shipment of each lot of components, containers, and closures that the PET production facility receives, including results of any testing performed.

VIII. PRODUCTION AND PROCESS CONTROLS

A. Regulatory Requirements

Proposed 21 CFR 212.50 would require adequate production and process controls to ensure consistent production of a PET drug product that meets the applicable standards for identity, strength, quality, and purity. Under proposed § 212.50(a), PET production facilities would be required to have written production and process control procedures to ensure and document that all key process parameters are controlled and that any deviations from the procedures are justified.

Proposed § 212.50(b) would require PET production facilities to have master production and control records that document all steps in the PET drug production process. Proposed § 212.50(b) also specifies what would be required in the master production and control records.

Proposed § 212.50(c) would require that a batch production record be generated from the master production record template for each new batch of a PET drug product. Each batch of a PET drug product would have to be uniquely identified, and its batch record would have to include each major production step, weights, and identification codes of components used, dates of production steps, identification of major equipment, testing results, labeling, initials or signatures of persons performing or checking each significant step in the operation, and results of any investigations conducted.

Proposed § 212.50(f) would require that when the results of the production of an entire batch of a PET drug product are not fully verified through finished-product testing or when only the initial sub-batch in a series is tested, the PET drug producer would have to demonstrate that the process for producing the PET drug product is reproducible and is capable of producing a drug product that meets the predetermined acceptance criteria. Process verification activities and results would have to be documented. Documentation would have to include the date and signature of the individual(s) performing the verification, the monitoring and control methods and data, and the major equipment qualified.

B. Master Production and Control Records/Batch Production and Control Records

Master production and control records are the principal documents describing how a product is made. The master production record serves as a template for all batch records, documenting how each batch will be produced. The designated individual should approve the master production and control records, or any changes to them, before they are implemented.

We recommend that the master production and control records present logical, chronological step-by-step instructions that document how the PET drug is to be produced.[6] Production should be discussed under headings, where applicable, such as accelerator operation, radiochemical synthesis, purification steps, and formulation of the finished product. We recommend the entire production process be pre-established and fully described in the master production and control record. The SOP in performing a specific step can be referenced. The master production and control records would include specifications for each critical step. Critical steps include the process step, process condition, or other relevant parameters that are controlled within predetermined criteria to ensure that the API meets its specification. Under proposed § 212.50(b), the master production and control records should include the following:

- The name and strength of the PET drug product in MBq/ml or mCi/ml (strength should be measured at a calibration time immediately after production)
- If applicable, the name and radioactivity or other measurement of each API as well as any inactive ingredient (e.g., diluent, stabilizer, or preservative) per batch or per unit of weight or measure of the drug product and a statement of the total radioactivity or measurement of any dosage unit
- A complete list of components designated by names and codes (component code) sufficiently specific to indicate any special quality characteristic
- Identification of all major equipment used in production of the drug product
- An accurate statement of the weight or measurement of each component (e.g., batch formula). In the process of producing FDG F 18, for example, multiple components are weighed or measured by volume. The radioactive component should be recorded in terms of radioactivity units.
- A statement of the action limit on radiochemical yield (i.e., the minimum percentage of yield beyond which investigation and corrective action would be required)
- Complete instructions (or references) for production, control, and testing of the PET drug. The synthesis of certain PET drugs, such as FDG F 18, involves multiple steps including drying, exposure to organic solvents, heating, pH adjustments, passage through purification media, and sterilizing filtration. We recommend there be a description of all in-process steps and their controls so that the operator can confirm that all steps are completed within specified conditions, where feasible. Controls for movement of liquids or gases should also be provided. For automated radiochemical synthesis equipment, it may be sufficient to reference the equipment manufacturer's manual that contains a full description of the automated production steps and controls.
- A description of the PET drug product containers, closures, and packaging materials, including a specimen or copy of each label and all other labeling.

[6] The draft guidance for industry *PET Drug Applications — Content and Format for NDAs and ANDAs*, which was issued in March 2000, will be available soon in final. Also, a sample format for a batch production and control record is available at *www.fda.gov/cder/regulatory/pet.*

Proposed § 212.1 defines a batch of a PET drug product as a specific quantity of PET drug product intended to have uniform character and quality. In the case of FDG F 18, a batch normally consists of the PET drug product produced in a single synthesis and purification operation. For ammonia N 13, a batch normally consists of multiple sub-batches having uniform character and quality, that are produced according to a single preparation order during one succession of multiple irradiation using a synthesis and/or purification operation.

Proposed § 212.50(c) would require the use of a batch record to document the production and testing of each batch. The batch records provide complete traceability and accountability for production and control of each batch. We recommend that information in the batch record (paper, or electronic copy) accurately reflect the information contained in the master production and control records. The control records may be cross-referenced and not be included as part of the batch record. The batch record is therefore a simplified version of the master production and control records that should contain the information needed for a documented history of the batch produced, including:

- Documentation of the execution of each critical production step (e.g., timed events occurred within specifications, heating steps occurred at the specified temperature, and ingredients were properly transferred into the reaction vessel) where feasible, taking radiation exposure concern into consideration. For automated radiochemical synthesis unit, the printout at the end of synthesis documenting the execution of the production steps and controls could be used for the chemical synthesis portion of the batch record.

- A compilation of tests and printouts that led to acceptance of the final product.

Under proposed § 212.50(c), information specific to batch production and control records would include the following:

- Name and strength of the PET drug product

- Unique identifier or number for each batch (an identifier or number also can be provided for each sub-batch produced)

- The name and radioactivity or other measure of each active pharmaceutical ingredient and each inactive ingredient per batch or per unit of radioactivity or other measurement of the drug product;

- Date and time of production steps

- Identification of major pieces of equipment where identical equipment in the facility can be used

- Actual weights (or measures) and identification codes of components used

- Labeling (a description of the finished drug product container label and the outer container label should be included)

- Initials or signatures of the person(s) performing and checking each significant step of the operation

- Results of any investigations conducted (this should include documentation of any deviations and follow-up investigations). Reference to the deviation and investigation reports can be indicated if stored separately.

- Results of testing

Batch records should include documentation that each significant step in the production was accomplished. When entries are made in batch records, an entry should be made directly after performing the activity (in the order performed) and would have to identify the person (signature or initials) making the entry. Corrections to paper entries would be dated and signed or initialed, leaving the original entry still readable. We recommend that each batch record be reviewed and approved for final release (signature/initials and date). For requirements and information on electronic records and signatures, interested persons should refer to Part 11 (21 CFR Part 11, Electronic Records; Electronic Signatures) and the Agency guidance on the scope and application of Part 11, Electronic Records; Electronic Signatures.[7]

C. Microbiological Control on Aseptic Processing and Sterilizing Filtration

Most PET drug products are designed for parenteral administration and are produced by aseptic processing. The goal of aseptic processing is to make a product that is free of microorganisms and toxic microbial byproducts, most notably bacterial endotoxins. The use of aseptic technique and control of microbiological impurities in components can eliminate microbial and endotoxin contamination from PET drugs. Aseptic processing of PET drugs should involve microbiological control over various types of components, as discussed below.

1. Water

Production processes that are relatively free of water or have rigorous chemical processes are unlikely to have microbial or endotoxin contaminants. PET production facilities often use *Water for Injection*, USP (WFI), an approved drug product. Using finished packaged WFI eliminates the need for the PET production facility to verify, maintain, and document a sterile water system.

Nonsterile water can develop significant microbial growth in a matter of days. We recommend that production processes that are water-intensive have sufficient controls to avoid microbial growth and development of biofilm (bacterial colonization). If nonsterile water is allowed to stagnate in a container or tubing, biofilm will develop. To minimize

[7] This draft guidance was issued in February 2003. Once finalized, it will represent the Agency's thinking on this topic.

their contact with nonsterile water, it is recommended that tubing and glassware be washed, rinsed, and promptly dried.

2. Glassware

Glassware and heat-resistant containers are relatively easy to keep free of microbial growth and pyrogens because they can be appropriately wrapped in foil and terminally sterilized by a suitable dry-heat cycle (see Section VI). Control procedures for these items should include prompt cleaning after use, rinsing with purified or WFI water, wrapping in aluminum foil, and depyrogenation by a suitable dry-heat oven cycle.

3. Transfer Lines

Transfer lines, which are used for synthesis and transfer of solvents or products, are usually made of durable plastic and are amenable to reuse. Prompt cleaning with organic solvents after use, rinsing with WFI, flushing with a volatile solvent, and drying with nitrogen are measures that help to control microbial contamination. Organic solvents such as ethanol and acetone are useful as a final rinse and are easily dried from containers or lines.

For PET drugs with a very short half life (e.g., ammonia N 13), sometimes a long fluid line is used to deliver multiple batches of the product solution to a remote area for further processing. We recommend that procedures be established to ensure that these fluid lines are clean and free of pyrogen contamination prior to each use.

4. Resin columns

Resin columns are a potential source of microbes and pyrogens because they can be contaminated with microorganisms. If available, the purchase of low-microbial grade resin material may limit bioburden. Material used for preparing resin columns should be suitably processed and rinsed with a large amount of WFI to control contamination. The prepared column should be appropriately flushed. Refrigerated storage is helpful in controlling contamination. We recommend that wet columns not be stored for a prolonged period of time.

5. Components

The selection of a reliable vendor and high-quality materials are effective ways to limit the risk of microbiological contamination. Components that support microbial growth during storage should be kept under controlled conditions and periodically assessed for microbial growth/ contamination.

6. Qualification for aseptic processing

Aseptic processing in PET drug production normally consists of, but is not limited to, (1) the aseptic assembly of the container/closure system (syringe, needle, sterilizing filter and vial) and (2) sterile filtration of the PET drug product. The ability of personnel to

perform aseptic processing can be assessed by conducting media fills. Simulations of aseptic manipulations (e.g., the aseptic assembly of the container system, vent connection, and sterile filtration) can be carried out by substituting a bacterial growth medium for the actual drug product. We recommend that an operator complete three successful media fill runs to qualify as a new operator. Each operator can be requalified annually by conducting one media fill run. Only personnel trained in aseptic techniques should conduct aseptic processing.

7. Sterilizing filtration

Even if care is taken to minimize microbiological contamination during synthesis, a drug is considered to be nonsterile until it is passed through a sterilizing grade filter. Generally, PET production facilities can use commercially available, presterilized filters to sterilize these solutions, provided that the vendor has been shown to be reliable, the filter is certified as compatible for the product, and it meets acceptable specifications.

Integrity testing of membrane filters should always be performed postfiltration. This is to ensure that the filter has performed according to specifications. Testing can be accomplished by performing the bubble-point test to show that the integrity of the filter was not compromised during or before use.

8. Environmental and personnel monitoring

Environmental monitoring is crucial to maintaining aseptic conditions. We recommend that microbiological testing of aseptic workstations be performed during sterility testing and critical aseptic manipulation. Methods can include using swabs or contact plates for surfaces and settling plates or dynamic air samplers for air quality.

D. Process Verification and Computer Control

Proposed § 212.50(f)(1) states that for PET drug production in which every batch undergoes full finished-product testing to ensure the PET drug product meets all specifications (e.g., F18 FDG), process verification is not required.

Proposed § 212.50(f)(2) would require that when the results of the production of an entire batch of a PET drug product are not fully verified through finished-product testing or when only the initial sub-batch in a series is tested, the PET drug producer would have to demonstrate that the process for producing the PET drug product is reproducible and is capable of producing a drug product that meets the predetermined acceptance criteria. Process verification activities and results would have to be documented. Documentation would have to include the date and signature of the individual(s) performing the verification, the monitoring and control methods and data, and the major equipment qualified. The determination not to conduct process verification should be supported by scientific rationale and data.

1. Process verification under 212.50(f) (2)

For a PET production facility that has an established history of PET drug production, the process verification can be accomplished using historical batch records, provided that there is adequate accumulated data to support a conclusion that the current process yields batches meeting predetermined acceptance criteria. We recommend that a comprehensive review of accumulated production, testing, and control data be conducted according to a written protocol defining the acceptable conditions. The accumulated data should verify that the process used was consistent and should document all changes to and failures of the process.

We recommend that new processes or significant changes to existing processes be shown to reliably produce PET drug products meeting the predetermined acceptance criteria before any batches are distributed. This verification should be conducted according to a written protocol and generally include at least three consecutive acceptable production runs.

Because PET drugs have short half lives, a PET producer may decide to evaluate the reliability of a new process or a significant change to an existing process to produce a PET product, meeting the predetermined acceptance criteria ***concurrently*** with the distribution of the batch. Such a decision should be justified in writing, subjected to quality control procedures, and performed according to a written protocol. Under this situation, we recommend each batch be processed in strict adherence to the written procedures, fully tested (except sterility testing), and found to comply with all procedural and quality test requirements prior to final release.

2. Computer control

Synthesis of some PET drugs can be executed under automated or computer control. We recommend that the computer program be verified before first use to demonstrate that it is suitable for its intended purposes and is capable of producing results that meet the predetermined acceptance criteria. We also recommend that subsequent changes or upgrades made to the computer program be documented and the process demonstrated to be capable of producing a PET drug product that meets the predetermined acceptance criteria. PET production facilities can rely on a certification by the software or system vendor that the specified software was verified under its operating conditions.

IX. LABORATORY CONTROLS

A. Regulatory Requirements

Proposed 21 CFR 212.60 would require the establishment and implementation of procedures for testing components, in-process materials, and finished PET drug products. All necessary tests of materials and products would have to be documented. Each laboratory would also be required to have sampling and testing procedures designed to ensure that components, drug product containers and closures, in-process materials, and PET drug products conform to appropriate standards. Analytical methods and test equipment would have to be suitable for their intended

uses. Reagents, solutions, and supplies used in testing procedures would have to be adequately controlled. The preventive maintenance, calibration, and procedures to make sure that the equipment is functioning properly would have to be documented. A complete record of all tests related to the production of a PET drug product would have to be kept to ensure compliance with established specifications and standards, including examinations and assays, as follows:

- A description of the sample received for testing, including its source, the quantity, the batch or lot number, the date (and time, if appropriate) the sample was taken, and the date (and time, if appropriate) the sample was received for testing.

- A description of each method used in the testing of the sample, a record of all calculations performed in connection with each test, and a statement of the weight or measurement of the sample used for each test.

- A complete record of all data (including graphs, charts, and spectra). For example, a print-out of the chromatogram with the calculated amounts of each component analyzed by the test

- A statement of results of the tests and their relation to acceptance criteria

- The initials or signature of the analyst and the date of the test

B. Laboratory Controls

Under proposed § 212.60, a PET production facility would have to have written test procedures that describe how to conduct each test of finished products and, where applicable, of components and in-process materials. Appropriate testing procedures would have to be established to ensure that PET drug products conform to appropriate standards, including established standards (e.g., relevant USP monographs) of identity, strength, quality, and purity. Analytical tests would have to be suitable for their intended purpose and have sufficient sensitivity, specificity, and accuracy.

We recommend that any new analytical test method be validated, through documented data, to show that it will consistently yield results that accurately reflect the quality characteristics of the product tested. The FDA and USP have published information for determining the appropriate analytical parameters (e.g., accuracy, precision, linearity, ruggedness) that should be used to validate a new method (see ICH *Q2A Text on Validation of Analytical Procedures* and USP General Chapter <1225> *Validation of Compendial Methods*). On the other hand, validation is not required for compendial methods.

If a USP analytical test method is used, a PET producer should verify that the method works under the actual conditions of use.

Most analyses use reference standards. We recommend that PET production facilities establish the reference standards identified in the analytical procedure or SOP. When a primary reference standard is obtained from an officially recognized source (e.g., USP), the material usually does not need further testing if it is stored under conditions consistent with the supplier's

recommendations. However, where an official standard is not available or if a PET production facility establishes its own reference standard, we recommend that data to fully confirm the material's identity and purity be established and documented. Documentation such as reference spectra or other supporting data to prove the identity and purity of the reference standard may be available from the supplier.

Under proposed § 212.60(f), equipment would have to be routinely calibrated and maintained according to the established written procedures (see Section VI). We recommend that PET production facilities verify that the equipment is in good working condition at the time the samples are analyzed. We also recommend that prior to each day of use of the HPLC and GC, a system suitability test using reference standards be conducted to verify that the resolution and reproducibility of the chromatographic system are adequate for the analysis to be done.

We recommend that any reagent or solution prepared on-site be adequately controlled (including temperature control, if applicable) and properly labeled with respect to identity, composition, and expiration date.

Raw test data (such as chromatograms, spectra, and printouts) and any calculations performed can be documented and become part of the batch production and control record. Records should have information such as the source of the test material, a description of the appearance of the material, the amount used, test and acceptance criteria, and an entry for data and interpretation of results. Laboratory controls should be followed and documented at the time of performance. We recommend that deviation from written procedures be documented and justified. Any out-of-specification results obtained should be investigated and documented.

X. STABILITY TESTING

A. Regulatory Requirements

Proposed 21 CFR 212.61 would require the establishment of a written stability testing program for each PET drug product. This program would have to be used to establish suitable storage conditions as well as expiration dates and times.

B. Guidance on Stability

As with other drug products, PET drug molecules are expected to remain stable during storage. Although PET drug products have extremely short shelf lives, because of their short half lives compared to other kinds of drug products, there are stability concerns due to radiation-related radiolysis. Certain PET drug products (e.g., F18 fluorodopa) can undergo very rapid chemical changes. Therefore, appropriate parameters should be evaluated to establish and document the stability of PET drug products under proposed storage conditions. Examples of stability parameters include radiochemical identity and purity (including levels of radiochemical impurities), appearance, pH, stabilizer or preservative effectiveness, and chemical purity. We recommend that appropriate stability-indicating methods that can distinguish degradation products and impurities be used. Stability testing of the PET drug product should be performed

at the highest radioactive concentration, and the whole batch volume in the intended container/closure should be stored. At least three production runs of the final product should be studied for a time period equal to the labeled shelf life of the PET drug product.

Although stability studies in support of an expiration dating period would be needed for approval of a PET drug product, subsequent changes to the expiration date could be made without prior approval (changes would be noted in the annual report for the drug product).

XI. FINISHED DRUG PRODUCT CONTROLS AND ACCEPTANCE CRITERIA

A. Regulatory Requirements

Proposed 21 CFR 212.70 would require that specifications be established and met for each PET drug product batch, including identity, strength, quality, purity, and, if appropriate, sterility. The proposed regulation would require the implementation of procedures to ensure that a product is not released until appropriate laboratory testing is completed, reviewed, and approved by an appropriate releasing authority.

Proposed 21 CFR 212.71 would require a PET production facility to reject PET drug products that fail to meet acceptance criteria. Procedures would have to be established to identify and segregate the product. There would have to be predetermined procedures for investigating the cause of the problem and preparing a timely report on the occurrence, including a description of the corrective action taken, where appropriate.

B. Finished Product Testing

Methods of PET drug production may differ from site to site. As a result, there may be specific impurities to assess depending on the method of production, such as kryptofix in FDG F 18. We recommend using approved NDA specifications, or the IND accepted specifications. Under proposed § 212.70, PET production facilities would have to ensure that each batch of PET drug product meets its established acceptance criteria, except for sterility (see subsection C below), before it is given final release.

C. Microbiological Tests for Sterile PET Drugs

Sterility testing would have to be started within 30 hours after the completion of PET drug production. If the sample for sterility testing is held longer than indicated (e.g., over the weekend), PET producers should demonstrate that the longer period does not adversely affect the sample and the test results obtained will be equivalent. The samples should be stored appropriately (e.g., under refrigeration). Verification of equivalent results can be accomplished by inoculation of USP indicator organism(s) and demonstrate that there is little, if any, loss in viability of the inoculated microorganism. The USP General Chapter <71> *Sterility Tests* provides information about media and incubation conditions.

We recommend that testing be conducted in a controlled area such as a laminar airflow workbench (LAFW) with clean-room apparel. Aseptic techniques should be used for sterility testing. The greatest risk of false-positive results arises in the sampling and transfer of the test aliquot from the vial to the media. It may be convenient to apply direct inoculation into commercial media. We recommend that the media be observed on days 3, 7, and 14 after inoculation, but it is prudent to observe the media more often during the first week of incubation.

The USP *Bacterial Endotoxins Test* (BET) (General Chapter <85>) should be performed for a sterile PET drug that is intended for injection. The BET contains gel-clot and rapid photometric methods for endotoxin measurement.

The product can be distributed under control after a pharmacopeial bacterial endotoxin test is initiated. However, the endotoxin results should meet the acceptance criteria before administering the product to humans.

If the result of any bacterial endotoxin test exceeds the acceptance limit, or if a sterility test is positive for microbial growth, we recommend a complete investigation be conducted immediately and documented. We recommend that corrective actions based on the results of the investigations be implemented promptly.

D. Accepting and Releasing a Batch (Lot)

We recommend the designated individual review all laboratory testing and documentation from the batch record to determine whether or not the PET drug product has met all acceptance criteria. If the product has met acceptance criteria, the designated individual with quality assurance function should sign and date the release sections of the batch record and sign a release for human administration.

In many cases, modifications to this standard procedure for product release may be appropriate. For example, transportation deadlines may justify a prerelease for distribution before all elements of testing and review are finalized. Other than sterility testing, all finished-product tests would have to be completed or in progress at the time of shipment or distribution and PET drug products can be released for distribution (but not administration) while some tests are pending. Under proposed § 212.70, these tests would have to be completed prior to final release for human administration. When it is determined that all acceptance criteria have been met, the PET production facility should then provide a notice of final release to the receiving facility so that the dose may be given to the patient. We recommend the establishment of effective procedures for immediate notification of the receiving facility if there is evidence of an out-of-specification result. Notification of the receiving facility due to product failure should be documented.

PET drugs that have a very short half life (e.g., ammonia N 13) can be produced in multiple sub-batches on the same day. End product testing of the initial sub-batch can be conducted, provided a sufficient number of sub-batches (beginning, middle, and end) have been demonstrated to produce a product meeting the predetermined acceptance criteria. For routine production in this circumstance, the release of subsequent sub-batches can be qualified if the initial sub-batch

meets all acceptance criteria. In certain cases, testing each sub-batch for certain attributes prior to release may be appropriate (e.g., for pH determination in ammonia N-13 production method using Devarda's alloy catalyst).

E. Conditional Final Release

When one of the required finished product tests cannot be completed due to a breakdown of the analytical equipment, proposed 212.70 (f) establishes criteria under which PET producers may still release the drug product for human use. If equipment is properly maintained, breakdowns should be a rare occurrence. We recommend that PET producers determine if the missing testing would adversely affect the safety and effectiveness of the PET drug product. Conditional release should be extremely infrequent. Only products that meets all conditional release criteria would be able to be released. Conditional release of a PET drug product would not be permitted if a PET drug producer could not perform a radiochemical identity/purity test on the active pharmaceutical ingredient of a PET drug product. All activities of conditional release would have to be documented.

F. Rejection and Reprocessing

Under proposed § 212.71(a), a batch of a PET drug product that fails to meet established specifications would have to be rejected, and procedures would have to be established to identify and segregate the product. Proposed § 212.71(b) would require that documentation of the investigation of a nonconforming product include the results of the investigation and final disposition of any rejected product.

Under proposed § 212.70 (d), a drug product can be reprocessed if pre-established procedures (set forth in production and process controls) are followed and the finished product conforms to specifications before final release. When the option for reprocessing is exercised, we recommend that the event be documented and conditions described in a brief deviation report. Examples of reprocessing could include a second passage through a purification column to remove an impurity, or a second passage through a filter if the original filter failed the integrity test.

XII. LABELING AND PACKAGING

A. Regulatory Requirements

Proposed 21 CFR 212.80 would require that:

- A PET drug product be suitably packaged and labeled to protect the product from alteration, contamination, and damage during the established conditions of storage, handling, and shipping.

- Labels and packaging operations be controlled to prevent labeling and product mix-ups.

- All information stated on each label be contained in each batch production record.

B. Recommendations on Labeling and Packaging

Regardless of the scope of operation of a PET production facility, we recommend that appropriate measures be taken to handle labels in a way that prevents mix-ups with any other labeling materials.

We recommend that PET drug products be labeled with adequate, legible identifying information to prevent errors during storage, shipment, and use.. Once an NDA or ANDA is approved for a PET drug product, the label approved in the NDA must be used. Prior to approval of the NDA or ANDA, the label should be approved by persons responsible for quality assurance procedures. Labels can be computer generated or handwritten.

Because of radiation exposure concern, it is a common practice to prepare much of the labeling in advance. For example, an empty product vial can be prelabeled with partial information (e.g., product name, batch number, date) prior to filtration of the radioactive product, and upon completion of QC test, the outer shielded container can be labeled with the required information (e.g., radioactivity). Alternatively, a string label can be used to label the immediate container provided that there is a way to associate the label with the vial if the label were to come off. Different approaches can be used as long as the approach ensures that the required information is available on the label. A label identical to that affixed to the container shield can be incorporated into the batch production record. A final check should be made to verify that the correct and complete label has been affixed to the container and the shield.

XIII. DISTRIBUTION

A. Regulatory Requirements

Proposed 21 CFR 212.90 would require the development of procedures to ensure that the shipment will not adversely affect the product. PET production facilities would have to maintain distribution records for PET drug products.

B. Recommendations

PET drug products should be shipped in accordance with labeled conditions (e.g., temperature) to ensure the identity, purity, or quality of the drug product. For PET production facilities distributing to outside clients or outside pharmacies, information on the method of shipment and the contact person at the final destination should be included. We recommend that a system be put in place by which the chain of distribution of each batch of PET drug product can be readily determined to permit its recall if necessary. A recall should consist of notifying the receiving facility, pharmacist, and the patient's physician, if known. When the receiving facility disposes of the recalled drug, the PET drug producer can obtain a notification from the receiving facility confirming the recalled drug has been disposed of and describing the manner in which it was disposed.

When the PET production facility ships the final released PET drug product supplied as a pharmacy bulk package (USP<1> *Injections)* to a nuclear pharmacy for dispensing into individual patient doses, FDA generally regards subsequent distribution of the drug product as part of the practice of pharmacy.

XIV. COMPLAINT HANDLING

A. Regulatory Requirements

Proposed 21 CFR 212.100 would require that procedures be developed and implemented for receipt and handling of all complaints pertaining to a specific PET drug product, including review by a designated individual to determine compliance with specifications and to initiate an investigation into the problem. A file for drug product complaints would have to be maintained. The file would have to contain the name and strength of the PET drug product, the batch number, the name of the complainant, the date the complaint was received, the nature of the complaint, and the response to the complaint. The file would also have to include the findings of any investigation and followup. A PET drug product implicated in a complaint could not be reprocessed and would have to be destroyed in accordance with applicable Federal and State law.

B. Recommendations

We recommend that the designated individual be responsible for collecting as much information as possible about the drug and the nature of a complaint and for completing an investigation of the matter as soon as possible. Corrective action should be taken immediately if there is any reason to believe that an adulterated drug was implicated in the complaint. Under proposed § 212.100(c), complaints would have to be maintained in a file designated for that purpose. We recommend that complaint files be easily retrievable for review and trending.

XV. RECORDS

A. Regulatory Requirements

Proposed 21 CFR 212.110(a) would require that all records be maintained at the PET production facility or another location that is reasonably accessible to responsible officials of the PET production facility and FDA investigators.

Proposed § 212.110(c) would require that all records referenced in part 212 be kept for at least 1 year from the date of final or conditional final release of a PET drug product.

B. Recommendations

The regulation would require that records be stored at a PET production facility or another location that is reasonably accessible. A reasonably accessible location is one that would enable

the PET production facility to make requested records available to an FDA investigator in a reasonable period of time during an inspection. The records would have to be legible and stored in a manner that prevents their deterioration and/or loss.

We recommend that forms for collecting data be kept to a minimum by designing multipurpose documents and eliminating redundancy, where possible. It is prudent to have as much of the required information within the batch production record as possible. Records can be kept electronically.

Other records that would have to be kept include information relating to the composition and quality of the PET drug product and operation of the production processes, such as laboratory records, out-of-specification results, master and batch records, distribution records, and complaint files. Records relevant to materials and PET drug products would have to be kept at least 1 year from the date of final or conditional final release. Verification reports should be kept as long as the systems are in use.

REFERENCES

FDA. *Guide to Inspection of Computerized Systems in Drug Processing.* February 1983.

FDA. *General Principles of Process Validation.* May 1987.

FDA. *Sterile Drug Products Produced by Aseptic Processing.* June 1987.

FDA. *Q2B Validation of Analytical Procedures: Methodology.* May 1977.

FDA. Q2A *Text on Validation of Analytical Procedures.* March, 1995.

FDA. *Reviewer Guidance — Validation of Chromatographic Methods*, November 1994.

FDA. 21 CFR Part 11; Electronic Records; Electronic Signatures. FR Notice 7/21/99 (64 FR 39146).

U.S. Pharmacopeia. <1> *Injections.* USP 26, NF 21, 2003.

U.S. Pharmacopeia. <71> *Sterility Tests*. USP 26, NF 21, 2003.

U.S. Pharmacopeia. <85> *Bacterial Endotoxins Test*. USP 26, NF 21, 2003.

U.S. Pharmacopeia. <621> *Chromatography.* USP 26, NF 21, 2003.

U.S. Pharmacopeia. <821> *Radioactivity*. USP 26, NF 21, 2003.

U.S. Pharmacopeia. <823> *Radiopharmaceuticals for Positron Emission Tomography-Compounding.* USP 26, NF 21, 2003.

U.S. Pharmacopeia. <1015> *Automated Radiochemical Synthesis Apparatus*. USP 26, NF 21, 2003.

U.S. Pharmacopeia. <1225> *Validation of Compendial Methods.* USP 26, NF 21, 2003.