Guidance

PET Drug Products – Current Good Manufacturing Practice (CGMP)

DRAFT GUIDANCE

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For questions regarding this draft document contact Brenda Uratani, 301-594-0098.

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

March 2002

Compliance

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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

I. INTRODUCTION

This draft guidance is intended to help PET drug producers better understand FDA's thinking concerning compliance with the preliminary draft proposed CGMP regulations if they were to become final after notice and comment rulemaking. The guidance addresses resources, procedures, and documentation for PET drug centers, large and small. In some cases, the guidance provides practical examples of methods or procedures that PET centers could use to comply with possible 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 In developing this draft guidance, FDA has taken into consideration relevant issues, concerns, and questions raised at the public meetings held with professional associations, producers of PET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.

Throughout this draft guidance, the term *proposed CGMP regulations* (or *requirements*) refers to regulations that are still being developed and will be formally proposed under the Agency's notice and comment rulemaking process. If appropriate, this draft guidance will be revised and republished for comment in parallel with the publication of the proposed regulations.

II. BACKGROUND

Section 121(c)(1)(A) of the Food and Drug Administration Modernization Act of 1997 (the Modernization Act) directs the Food and Drug Administration (FDA) to establish current good manufacturing practice (CGMP) requirements for positron emission

[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).

tomography (PET) drugs. In the future, FDA will be proposing such requirements under 21 CFR Part 212. In 1999, FDA published a preliminary draft of the proposed PET CGMP regulations (see FDA's Web site at www.fda.gov/cder/fdama/212draft.htm and notice of availability, 64 FR 51274; September 22, 1999). The FDA received comments on the preliminary draft at a public meeting on the subject (September 28, 1999). The FDA has made changes in the working draft in response to the public comments. A revised preliminary draft of the CGMP regulations is being published in conjunction with this draft guidance. This draft guidance provides more details for discussion purposes on acceptable approaches to complying with the regulations if they were to be published in final form.

As directed by Congress in the Modernization Act, to aid our development of this proposed regulation, 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 centers 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 centers located in universities and similar not-for-profit institutions. An academically oriented PET center is usually characterized by the production of 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 centers are now operated by large, 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 centers are not affiliated with any university or hospital. These for-profit, often contractually managed, and independently operated PET centers distribute PET drug products to significantly greater numbers of patients, sometimes hundreds of miles from the production site.

Our review of PET drug production leads us to conclude that a PET drug producer's status as either a not-for-profit or for-profit entity does not have a significant 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 center 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 also found that certain production standards and controls are necessary to ensure the production of quality PET drugs regardless of differences in the nature and scope of production among PET centers. The Agency believes that the welfare of any particular patient undergoing a PET scan should not depend on where a particular PET drug was manufactured.

The preliminary draft proposed regulation on CGMP requirements contains the minimum standards that we believe are needed for PET drug production at all types of PET centers. We have designed the CGMP regulations to be sufficiently flexible to accommodate not-for-profit, academically oriented institutions that make PET drug products for their own patients and research use as well as larger commercial producers that serve a greater number of patients in a broader region.

To assist PET centers in understanding the preliminary draft proposed CGMP regulations, we are developing this guidance. For many aspects of CGMP, including matters such as resources, controls, and documentation, the draft guidance makes different recommendations depending on the size, scope, and complexity of a PET center's operations. The draft guidance provides practical examples of methods and procedures that different types of PET centers could use to comply with the preliminary draft CGMP requirements.

The preliminary draft proposed regulation also incorporates 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), 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. 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.

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^+) and is used for the purpose of providing 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 represents all doses to be administered, is tested to verify that the batch or the lot conforms to all established specifications.

A finished 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 use 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 are CGMPs?

Manufacturing practices are the methods, facilities, and controls used in the preparation, processing, packaging, or holding of a drug. A current good manufacturing practice (CGMP) is a minimum standard that ensures the drug meets the requirements of safety and has the identity strength, quality, and purity characteristics it is represented to possess. CGMPs are 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., NRC and state and local agencies). Documents produced for others, where appropriate, can be used to provide the documentation of compliance with CGMPs. 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, supplemental documentation should be developed.

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, and 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).[2]

FDA has determined that the production of a PET drug product would include all operations to the point of final release of a finished dosage form (includes unit dose containers, multiple dose containers and pharmacy bulk packages), and these activities would be subject to CGMPs. After a distributed PET drug product is received by the receiving facility for administration to patients, FDA generally regards subsequent use of the drug product as part of the practice of medicine and pharmacy. FDA generally will defer to State and local authorities concerning regulation of such activities.

[2] Congress specifically exempted PET drugs from the provisions on pharmacy compounding in section 127 of the Modernization Act (section 503A(e)(1) of the Act)). The U.S. Court of Appeals for the Ninth Circuit declared section 503A to be invalid in its entirety. FDA petitioned the court for a rehearing but this request was denied; the U.S. Supreme Court has granted a petition for certiorari. Pending a decision by the Supreme Court, it is FDA's position that section 503A is invalid only in the Ninth Circuit. Regardless, the approval procedures and CGMP requirements that FDA is developing will be applicable to all PET drugs.

Although not part of production, the distribution of PET drug products also would be subject to CGMP requirements. In general, a routine FDA inspection to ensure compliance with CGMP would focus on activities up to the point of final release of a PET drug product.

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

III. PERSONNEL RESOURCES

A. Regulatory Requirements

Preliminary draft proposed 21 CFR 212.10 would require a PET center 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.

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

B. Organization and Staffing

Staffing levels should correspond to the size and complexity of the operation of the PET center. Staffing levels should enable a PET center to satisfactorily complete all intended tasks in a timely manner. Regardless of the size, scope, or complexity of the operation, there should be clearly written policies describing how the production and quality control units (those persons with authority and responsibility to oversee the process; see Section IV) are staffed and managed. The organizational structure of the PET center and the responsibilities and assigned duties of all staff should be identified.

For a PET center that typically produces a few doses daily of a PET drug for its own patients, it may be adequate to employ one or two persons to accomplish all production and quality control functions. The PET center should demonstrate that the production and quality control functions can be consistently accomplished in a timely and acceptable manner. 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

center with only one person assigned to perform production and quality control tasks, that person should check and recheck his or her own work. Self-checks involve the repetitive confirmation of the operator's own action and should be documented. Examples of self-check activities include reviewing batch records before release of the drug product for distribution and verifying calculations in analytical tests.

At a PET center that produces larger quantities and/or multiple PET drugs, the staffing level should be adequate to manage production and quality control functions. As production operations become larger and more complex, the potential for error, mix-ups, and/or contamination increases. Personnel should, therefore, be assigned to conduct second-person checks to verify each critical step in production and quality control.

C. Personnel Qualifications

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

PET centers should maintain an updated file (e.g., curriculum vitae, copies of degree certificates, certificate of training) for each employee.

IV. QUALITY CONTROL

A. Regulatory Requirements

Preliminary draft proposed 21 CFR 212.20 would require PET centers to have a quality control unit. Under the proposed regulations, the quality control unit would have the authority and responsibility to perform the following tasks.

- 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 and approve or reject PET drug products

- 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 Quality Control Unit

The quality control unit should be the final decision making body on matters within its area of responsibility. The quality control unit should examine each lot of incoming material to ensure that the correct material is received in good condition and is properly identified and stored. Before any material is released for production, the quality control unit should ensure that the material meets its established specifications. Such evaluation can include testing of the material (see Section VI, Control of Components, Containers, and Closures).

The quality control unit should ensure that procedures and specifications affecting production and testing of a PET drug product are adequate for their intended purposes. Procedures and specifications should be reviewed and approved by the quality control unit prior to their implementation.

The quality control unit also should approve proposed changes to procedures or specifications before they are implemented. The quality control unit should investigate errors and ensure that appropriate corrective action is taken to prevent their recurrence.

The quality control unit should review the production batch records and laboratory control records for conformance to established specifications before authorizing the final release or rejection of a batch or lot of PET drug product

The staffing and responsibility of the quality control unit should be consistent with the recommendations provided in Section III of this guidance. Small PET centers are encouraged to use an outside consultant or an independent expert to periodically audit performance of quality control functions. In large PET centers, the quality control unit should be independent from the production unit. Decisions made by the quality control unit to reject batches should not be subject to further review or revocation by another organizational unit or person.

V. FACILITIES AND EQUIPMENT

A. Regulatory Requirements

Preliminary draft proposed 21 CFR 212.30(a) would require that a PET center 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 an orderly operation during the production process. It should also effectively protect the product from contamination originating from personnel and surrounding areas. The 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 that should be considered include particulate matter and chemical and microbiological materials. The lead-based radiation shielding should be properly covered to prevent lead contamination of the product.

Phases of production with the potential for microbiological contamination should be performed under appropriate environmental conditions that prevent 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.

Related work areas should also 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 small PET centers, 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 separately from quarantined or approved materials.

In large PET centers having relatively complex operations, 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. Large PET centers that handle large numbers of components and PET drug products should organize their production facilities in such a way as to prevent mix-ups and contamination. 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 Facility

The aseptic work area should be suitable for the preparation of a sterile PET drug product. Air quality in the aseptic processing area should be adequately 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 with a rating of Class 100 (e.g., a LAFW or barrier isolator). Examples of such activities include (1) the aseptic assembly of sterile components (syringe, needle, filter and vial) for sterile filtration of the PET drug product, (2) storage of the sterility samples, and (3) sterility testing of the finished PET drug product. The following precautions should be taken to maintain the appropriate air quality of the aseptic workstation:

- The aseptic workstation should be sanitized before each operation.

- Container assemblies should be prepared at the beginning of the day before other daily activities begin and before additional personnel have entered the room.

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

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

- Gloved hands should be frequently sanitized when working in the aseptic workstation. Gloves should be 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) should be sanitized and wiped with an appropriate disinfectant (e.g., 70 percent isopropyl alcohol) before being placed in the aseptic workstation.

Conditions in the room where aseptic manipulations are conducted should not present a challenge to the operating capability of the aseptic workstation. For example, the room should not be carpeted and should have no 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 sanitized and capable of withstanding frequent sanitizing. Cleaning and sanitizing should be performed frequently to ensure sufficient and 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 should be appropriate for the performance of its intended function and should not contaminate the product. Each piece of equipment should be suitably located to facilitate its use, cleaning, and maintenance. The PET center should 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.

Each PET center should select suitable cleaning agents and cleaning techniques and ensure that their cleaning operations do not contaminate the drug product.

Newly acquired equipment should be qualified before first use to verify that it was installed correctly and is capable of operating as intended.

There should be 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. Calibration checks recommended by equipment manufacturers should be followed unless the PET center has determined that more frequent calibrations are needed. Major repairs or upgrades in equipment may warrant requalification. Malfunctioning or incorrectly operating equipment should not be used 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 a number of PET centers may continue to use existing equipment when they become subject to the requirements of the final CGMP regulations. PET centers should make sure that the existing equipment is working properly and is being maintained and calibrated according to written procedures.

Representative equipment is discussed below to illustrate how it might be controlled in a PET center.

a. Automated radiochemical synthesis apparatus

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

Prior to the production of a PET drug product batch, the operator should conduct a performance check to ensure the following:

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

- All the 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 should ensure that the system is functioning and recording correctly and that the correct program and operational parameters are used.

b. Aseptic Workstation

The aseptic workstation provides an appropriate environment for aseptic procedures. Examples of workstations include a laminar air flow workbench (LAFW) or barrier isolator system. An integrity test should be conducted at installation (including after each change of the high-efficiency particulate air (HEPA) filter) to ensure proper performance. Certification of the aseptic workstation should 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.

A qualified operator should 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. The filter should be changed when clogging is detected.

Laminar airflow velocities should 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. Operators should be trained on the importance of minimizing objects and equipment within the critical area so laminar airflow is not disrupted.

c. Electronic or analytical weight balance

Written procedures should be available describing the proper use of the balance, assessment of accuracy, and a schedule for calibration. Performance should be checked by weighing two or more standard weights on each day of use. The calibrated weights used for assessing daily performance should bracket the range of the weights being measured. The balance should be fully calibrated periodically, or upon failure to meet daily performance checks.

d. Dry-heat ovens

If glassware and heat-stable materials are depyrogenated and sterilized on-site, the PET center should validate 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 should involve 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, the operator should 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

The temperature and humidity (where appropriate) of the dry heat oven, refrigerator, freezer, and incubator should 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

A PET center should have the necessary 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 its use, the analyst should make sure that the GC system is functioning correctly. Appropriate system suitability testing procedures and criteria (see USP General Chapter <621> *Chromatography*) should help ensure the correct performance of the GC system.

b. High performance liquid chromatograph (HPLC)

The HPLC system should have detectors that are suitable for the intended purpose. The detector should be of sufficient sensitivity, and prior to its use, the analyst should make sure that the HPLC system is functioning correctly. System suitability testing procedures and criteria (see USP General Chapter <621> *Chromatography* and FDA reviewer guidance, *Reviewer Guidance — Validation of Chromatographic Methods* (November 1994) should help to ensure the correct performance of the HPLC system.

c. Dose calibrator

A dose calibrator that gives a printout should be used and tested for (1) accuracy at installation and at least annually thereafter using at least two NIST traceable sealed sources in the energy range that covers the energy of the PET radioisotope; (2) linearity in the range of measurement upon installation and at least quarterly thereafter; (3) geometry dependence, over the range of volumes and volume configurations, at installation; and

(4) precision on a daily basis. Nuclear Regulatory Commission regulations (under 10 CFR 35.50) should be followed for the procedure and acceptable criteria for the above calibrations.

d. Radiochromatogram scanner

A radiochromatogram scanner (or equivalent equipment that provides a radiochromatogram) should be used for the measurement of radioactivity distribution in the developed thin layer chromatography plate (e.g., ITLC, paper or plate). The scanner should have sufficient sensitivity and spatial resolution for the intended discriminatory and quantitative objective. Manufacturers' 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) should be useful for the determination of radionuclidic purity and for the identification of the radionuclide. The overall system should have sufficient sensitivity and resolution for the intended purpose (see USP General Chapter <821> *Radioactivity*). Adequate calibration using 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.

VI. CONTROL OF COMPONENTS, CONTAINERS AND CLOSURES

A. Regulatory Requirements

Preliminary draft proposed 21 CFR 212.40(a) and (b) would require PET centers 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 centers keep a record of each shipment of each lot of components, containers, and closures that they receive.

B. Control of Components, Containers, and Closures

Written procedures should be established specifying how each material (components, containers, and closures) will be selected and controlled in PET centers. 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

Only qualified vendors should be used. A vendor becomes qualified when there is evidence to support its ability to supply a material that consistently meets all quality specifications. PET centers should obtain assurance from a vendor that the vendor will 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

Each lot of material should 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 should be used in the disposition of that lot. Sufficient information should be documented to enable the PET center to have full accountability and traceability of each lot. Before release for use, incoming materials should be segregated and placed under quarantine. 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 center's current specification sheet to ensure that acceptance criteria are met. At a minimum, certain components described below (see Acceptance Testing) should 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 center’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.[3] Approved materials should be labeled *Approved* with an identifying code number, storage conditions, and expiration date. Materials should be stored under the proper storage conditions and in an area designated for approved materials. If a lot is rejected, it should be labeled *Rejected*, segregated, properly disposed of, and each of these actions should be documented.

An item should 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. PET centers should 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

PET centers should 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 shipment of incoming materials should be examined to ensure that all specifications are met. The use of an identity test is recommended, but not required. Most PET centers currently employ micro-scale chemistry and use relatively small amounts of solvents or reagents in the automated radiochemical synthesis. The amount of solvents or reagents in the finished product is typically reduced or eliminated during production or purification procedures. Residual reagents, process impurities, and solvents can be identified during finished product testing.

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

Under proposed § 212.40(c), PET centers would have to conduct identity testing on each lot of a component that yields an API and on each lot of inactive ingredient. In addition, each lot of such a component or an inactive ingredient would have to be tested for conformity with written specifications. PET centers that do not perform such testing can accept a lot on the basis of a COA on that lot from the supplier provided that they have established the reliability of the supplier's test results and that they perform at least one identity test on each such lot received. In those cases when specific tests exist, they should be used. The reliability of the

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

supplier's test results can be established by conducting independent testing and confirmation of the testing results for the first three lots of the components received and at appropriate intervals thereafter (e.g., semiannually or because of a change in specifications).

Following are examples of testing of components that yield an API:

- For the production of fludeoxyglucose F 18 injection (FDG F 18), the components that yield the API are O 18 water and mannose triflate. A reaction-based identity test for O 18 water is the production of F 18 by nuclear bombardment. Alternatively, the identity of O 18 water can be established by mass spectroscopy. A specific identity test can be performed on mannose triflate using infra red spectroscopy (IR) or nuclear magnetic spectroscopy (NMR) analysis.

- In instances when F 18 fluoride is obtained from outside suppliers, a PET center should establish appropriate acceptance procedures that include examination of the COA to ensure that each lot is acceptable for use in PET drug product production.

- If the target material (O 18 water) is recycled, approved, and validated, procedures on how the reprocessed lot can be accepted for use should be established and used.

The inactive ingredients in PET drugs usually consist of a diluent, a stabilizer, and/or a preservative. Under proposed § 212.40(c)(1), 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) also states that if an inactive ingredient (e.g., 0.9% sodium chloride solution) were prepared on site, an identity test on the components used to make the inactive ingredient would have to be performed before they were 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

PET centers should use approved and reliable sources for these items. Under proposed § 212.40(c)(3), a visual identification of each lot of containers and closures would have to be conducted. A COA showing conformance with the established specifications should be obtained before accepting each lot of the container/closure system. The container/closure system should 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, validation of the efficacy of each process should be demonstrated. Validated procedures should be used in such cases.

5. Handling of components, containers, and closures

When the quality control unit has determined that a lot of material has met all acceptance criteria, the material should 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 would have to 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 center receives, including results of any testing performed.

VII. PRODUCTION AND PROCESS CONTROLS

A. Regulatory Requirements

Preliminary draft 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 centers 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 centers to have a master production and control record that documents all steps in the PET drug production process, and specifies what would be required in the master production and control record.

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 be uniquely identified, and its batch record would include each production step, weights, and identification codes of components used, dates of production steps, identification of major equipment, testing results, labeling, names of persons performing or checking each significant step in the operation, and any investigations conducted.

Proposed § 212.50(f) would require that the process for producing each PET drug product be validated according to established procedures. Validation activities and

results would have to be documented. The quality control unit would have to approve the validation process and the results.

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

A master production and control record is the principal document describing how a product is made. It serves as a template for all batch records, documenting how each batch should be produced. The quality control unit should approve the master production and control record, or any changes to it, before it is implemented.

Suitable controls should be initiated to consistently produce a product with the desired quality attributes. The master production and control record should present logical, chronological step-by-step instructions that document how the PET drug is to be produced.[4] Production can be discussed under headings, where applicable, such as accelerator operation, radiochemical synthesis, purification steps, and formulation of the finished product. The entire production process should be pre-established and fully described in the master production and control record, which also should identify the equipment and instrumentation that will be used in a specified and controlled manner as part of the approved production process. The master production and control record should include valid specifications for each critical step. Under proposed § 212.50(b), the master production and control record 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 weight or measurement of each API per batch or per unit of weight or measure of the drug product and a statement of the total weight 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

[4] A draft guidance for industry, entitled *PET Drug Applications — Content and Format for NDAs and ANDAs,* was published in March 2000. Once finalized, that guidance will represent the Agency's current thinking on this subject. Also, a sample format for a batch production and control record is available at *www.fda.gov/cder/regulatory/pet.*

- A statement of the action limit on radiochemical yield (i.e., the maximum and minimum percentages of yield beyond which investigation and corrective action are required)

- Complete instructions 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. There should be a description of all in-process steps and their controls so that the operator and quality control unit can confirm that all steps are completed within specified conditions, where feasible. Controls for movement of liquids or gases should also be provided.

- A description of the PET drug product containers, closures, and packaging materials, including a specimen or copy of each label and all other labeling.

A batch of a PET drug product is a predefined quantity of the drug that has been produced 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, and they 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. Information in the batch record should be an accurate reproduction (paper, or electronic copy) of the master production record. The batch record should be a check list documenting, for example, that all processing steps and their controls were carried out, timed events occurred within specifications, heating steps occurred at the specified temperature, and ingredients were properly transferred into the reaction vessel. The batch record also should contain a compilation of tests and printouts that led to acceptance of the final product. The batch production and control record enables an operator to fully document and establish traceability to specific lots of all components, containers/closures, and equipment used in the production of the PET drug.

Under proposed § 212.50(c), information specific to a batch record would include the following:

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

- Dates of production steps

- Identification of major pieces of equipment used in the manufacturing

- 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)

- Identification 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)

- Results of finished PET drug product testing

When entries are made in batch records, an entry should be made directly after performing the activity (in the order performed) and should identify the person (signature or initials) making the entry. Corrections to paper entries should be dated and signed or initialed, leaving the original entry still readable. Corrections to electronic records should be recorded according to Part 11 (21 CFR Part 11, Electronic Records; Electronic Signatures), and there should be an audit trail to document the changes. Each batch record should be reviewed and approved for final release (signature/ initials and date).

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 content or have rigorous chemical processes are unlikely to have microbial or endotoxin contaminants. PET centers often use *water for injection*, USP (WFI), an approved drug product. Using finished packaged WFI eliminates the need for the PET center to maintain and validate a sterile water system.

Nonsterile water can develop significant microbial growth in a matter of days. Production processes that are water-intensive should 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. Tubing and glassware should be washed, rinsed, and promptly dried to minimize their contact with water.

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 V). 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. These fluid lines should be clean and free of pyrogen contamination for their duration of use.

4. Resin columns

Resin columns are a potential source of microbes and pyrogens because they can carry 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. Wet columns should 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

Only personnel trained in aseptic techniques should conduct aseptic processing. Personnel performing aseptic processing should be qualified by media fill, which is a simulation of the production process.

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, filter and vial) and (2) sterile filtration of the PET drug product. Prospective operators can qualify for aseptic processing by performing media fill runs using bacterial growth media instead of the actual drug product. An operator should complete three successful media fill runs to qualify as a new operator. Each operator should be re-qualified annually.

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 centers can use commercially available, pre-sterilized 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.

Before using filters from a particular lot, a sample should be tested for integrity to demonstrate that the membrane has the ability to retain microorganisms. The manufacturer's recommended method can be used. In addition, the integrity testing of the membrane filter should be performed postfiltration to ensure that the filter has performed according to specifications. This 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. Microbiological testing of the aseptic workstation should be performed periodically. Methods can include using swabs or contact plates for surfaces, and settling plates or dynamic air samplers for air quality.

D. Process Validation and Computer Control

Preliminary draft proposed § 212.50(f) would require that PET drug production processes be validated to ensure that they are capable of consistently producing a product that meets all specifications. For a PET center that has an established history of PET drug production, validation of the production processes can be conducted

retrospectively, provided that the current process is supported by adequate accumulated data to support a conclusion that the process is normally sufficiently capable of yielding batches meeting predetermined specifications. Successful retrospective validation involves a comprehensive review of accumulated production, testing, and control data according to a written protocol defining the acceptable conditions. The accumulated data should be sufficient to verify that the process used was consistent and should consider all changes to and failures of the process.

Ideally, validation of a new process, or a significant change to an already validated process, would be shown prospectively (i.e., before any batches are distributed). As with retrospective validation, prospective validation should be conducted according to a written protocol and generally include at least three consecutive acceptable production runs.

Due to the short half-lives of PET drugs, a PET producer may decide to validate a new process or significant change to a validated process ***concurrently*** with the distribution of each validation batch. The decision to rely on concurrent validation should be justified in writing and approved by the quality control unit, and, as with any validation, performed according to a written protocol. Each batch subject to a concurrent validation protocol should be processed in strict adherence to the written procedures, fully tested (except sterility), and found to comply with all procedural and quality test requirements prior to final release. The PET producer should weigh the risks and benefits carefully in considering which type of validation scheme to follow, giving preference to validating prospectively, then retrospectively, and finally concurrently.

Synthesis of some PET drugs can be executed under automated or computer control. In such cases, the computer program should be validated to demonstrate that it is suitable for its intended purposes and is capable of producing valid results. For example, the computer program used in the automated synthesis of FDG F 18 can be validated by demonstrating that acceptable production criteria for the PET drug product are met for at least three consecutive production runs. Subsequent changes or upgrades made to the computer program should be revalidated. PET centers can rely on a certification by the software or system vendor that the specified software was validated and verified under its operating conditions.

Computerized systems should have sufficient controls to prevent unauthorized access or changes to data. There should be a record of any data change made, the previous entry, who made the change, and when the change was made. A back-up system should be available in case of system breakdown.

VIII. LABORATORY CONTROLS

A. Regulatory Requirements

Preliminary draft 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 (including source, batch or lot number, date, and time the sample was received for testing)

- A description or reference (e.g., standard operating procedure) to each method, including any calculations or weight or measurement of the sample used for each test

- A complete record of all data (including graphs, charts, and spectra)

- 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 center would have to have written test procedures (see FDA recommendations on standard operating procedures (SOP)[5]) that describe how to conduct each test for components, in-process materials, and finished products. Appropriate sampling and 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. If a USP analytical test method is used, it should be verified that the method works under the actual conditions of use.

Alternate testing methods can be used, provided the PET center has demonstrated at least equivalency to the regulatory method. Analytical test methods should be validated. The FDA and USP have published information for determining the appropriate analytical parameters (e.g., accuracy, precision, linearity, ruggedness) that

[5] Recommendations on SOP are available at *www.fda.gov/cder/regulatory/pet*.

should be used to validate a method (see ICH *Q2A Text on Validation of Analytical Procedures* and USP General Chapter <1225> *Validation of Compendial Methods*).

Most analyses use reference standards. PET centers should 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, if a PET center establishes its own reference standard, data to fully confirm the material's identity and purity should 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 V). PET centers should verify that the equipment is in good working condition at the time the samples are analyzed.

Any reagent or solution prepared on-site should 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 should 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. Deviation from written procedures should be documented and justified. Any out-of-specification results obtained should be investigated and documented.

IX. STABILITY TESTING

A. Regulatory Requirements

Preliminary draft 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

The PET drug molecule should remain stable during the course of storage of the PET drug product. Appropriate parameters should be evaluated to establish and document the stability of a PET drug product under proposed storage conditions. Examples of stability parameters include radiochemical identity and purity, appearance, pH, stabilizer

or preservative effectiveness, and specific activity. Appropriate stability-indicating methods that can distinguish degradation products and impurities should 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.

X. FINISHED DRUG PRODUCT CONTROLS AND ACCEPTANCE CRITERIA

A. Regulatory Requirements

Preliminary draft 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 center to reject PET drug products that fail to meet acceptance criteria. The quality control unit would have 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 one site to another; therefore, there may be specific impurities to assess depending on the method of production, such as kryptofix in FDG F 18. Approved NDA specifications, or the IND accepted specifications, should be used. Under proposed § 212.70, PET centers would have to ensure that each batch of PET drug product meets its established acceptance criteria, except for sterility (see Section X.C), before it is given final release.

C. Microbiological Tests for Sterile PET Drugs

The USP General Chapter <85> *Bacterial Endotoxins Test* (BET) should be performed for a sterile PET drug that is intended for injection. The harmonized BET in Supplement 2 of USP 24 NF 19 contains gel-clot and photometric methods for endotoxin measurement.

The USP General Chapter <71> *Sterility Tests* provides information about media and incubation conditions. Sterility testing should be performed within a day after the completion of PET drug production in a controlled area such as an 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. The media should be observed after days 3, 7, and 14 after inoculation, but it is prudent to observe the media more often during the first week of incubation.

If the result of any BET exceeds the acceptance limit, or if a sterility test is positive for microbial growth, a complete investigation should be conducted immediately and documented. Corrective actions based on the results of the investigations should be implemented promptly.

D. Accepting and Releasing a Batch (Lot)

The quality control unit or designate should 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 quality control unit should sign and date the release sections of the batch record and sign a release for human administration. In a larger PET center where there is a separate quality control unit, decisions made by the quality control unit to reject batches should not be subject to further review or revocation by another organizational unit.

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 end-product tests should be completed or in progress at the time of shipment or distribution. 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 center should then provide a notice of final release to the receiving facility so that the dose can be given to the patient. There should be effective procedures for immediate notification of the receiving facility if there is evidence of an out-of-specification result and for documenting the fate of such a drug product.

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 validated. 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. 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 the quality control unit would have 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 may be reprocessed if preestablished 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, the event should 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.

XI. LABELING AND PACKAGING

A. Regulatory Requirements

Preliminary draft proposed 21 CFR 212.80 would require that:

- A PET drug product be suitably packaged and labeled to ensure that the integrity of the product is maintained during 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 center, appropriate measures should be taken to handle labels in a way that prevents mix-ups with any other labeling materials.

A PET drug product should be labeled with adequate, legible identifying information to prevent errors during storage, shipment, and use. Labels can be computer generated or handwritten.

A string label can be used by PET centers 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 should be incorporated into the batch production record. A final check should be made to verify that the correct label has been affixed to the container and the shield.

For PET centers producing and distributing a large volume of PET drugs, the quality control unit should verify the contents of each label for accuracy and completeness.

XII. DISTRIBUTION

A. Regulatory Requirements

Preliminary draft proposed 21 CFR 212.90 would require the development of procedures to ensure that only PET drug products that have been suitably released will be shipped and that the shipment will not adversely affect the product. PET centers would have to maintain distribution records for PET drug products.

B. Recommendations

For PET centers distributing to affiliated institutions, outside clients, or outside pharmacies, information on the method of shipment and the contact person at the final destination should be included. A system should be in place by which the distribution of each batch of PET drug product can be readily determined to permit its recall if necessary. A recall would 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 should obtain a signed statement from the receiving facility confirming the recalled drug has been disposed of and describing the manner in which it was disposed.

XIII. COMPLAINT HANDLING

A. Regulatory Requirements

Preliminary draft 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 the quality control unit 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 a complete record of the drug involved, the complainant, the nature of the occurrence, and the investigation and response to the complaint. 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

The quality control unit should 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. Complaint files should be easily retrievable by the quality control unit for review and trending.

XIV. RECORDS

A. Regulatory Requirements

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

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

B. Recommendations

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

Forms for collecting data should 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 should 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 release. Validation 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. <71> *Sterility Tests*. USP 24 NF 19, 2000

U.S. Pharmacopeia. <85> *Bacterial Endotoxins Test*. USP 24 NF 19, Supplement 2, 2000.

U.S. Pharmacopeia. <823> *Radiopharmaceuticals for Positron Emission Tomography – Compounding.* USP 24 NF 19, 2000.

U.S. Pharmacopeia. <1015> *Automated Radiochemical Synthesis Apparatus*. USP 24 NF 19, 2000.

U.S. Pharmacopeia. <621> *Chromatography.* USP 24 NF 19, 2000.

U.S. Pharmacopeia. <821> *Radioactivity*. USP 24 NF 19, 2000.

U.S. Pharmacopeia. <1225> *Validation of Compendial Methods.* USP 24 NF 19, 2000.