

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 212

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Current Good Manufacturing Practice for Positron Emission Tomography Drug Products; Preliminary Draft Proposed Rule; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of availability of preliminary draft proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is announcing the availability of a preliminary draft proposed rule on current good manufacturing practice (CGMP) for positron emission tomography (PET) drug products. We are developing CGMP regulations for PET drug products in accordance with the Food and Drug Administration Modernization Act of 1997 (Modernization Act). We are making a preliminary draft of a proposed rule available to allow full discussion of its contents at an upcoming public meeting on CGMP requirements for PET drug products. We are announcing the availability of a companion draft guidance on CGMP for PET drug products elsewhere in this issue of the **Federal Register**.

DATES: A public meeting on the preliminary draft proposed rule will be held on May 21, 2002. Submit written or electronic comments on the preliminary draft proposed rule by June 5, 2002.

ADDRESSES: A copy of the preliminary draft proposed rule will be on display at the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit written requests for single copies of the preliminary draft proposed rule to the Division of Drug Information (HFD-240), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. Send one self-addressed adhesive label to assist that office in processing your request. See the **SUPPLEMENTARY INFORMATION** section for electronic access to

the preliminary draft proposed rule. Submit written comments to the Dockets Management Branch (address above). Submit electronic comments to <http://www.fda.gov/dockets/ecomments>.

FOR FURTHER INFORMATION CONTACT: Brenda Uratani, Center for Drug Evaluation and Research (HFD-325), Food and Drug Administration, 7520 Standish Pl., Rockville, MD 20855, 301-594-0098.

SUPPLEMENTARY INFORMATION:

I. Background

On November 21, 1997, the President signed the Modernization Act (Public Law 105-115) into law. Section 121(c)(1)(A) of the Modernization Act directs us to establish appropriate approval procedures and CGMP requirements for PET drugs. Section 121(c)(1)(B) states that, in adopting such requirements, we must take due account of any relevant differences between not-for-profit institutions that compound PET drugs for their patients and commercial manufacturers of such drugs. Section 121(c)(1)(B) also directs us to consult with patient advocacy groups, professional associations, manufacturers, and physicians and scientists who make or use PET drugs as we develop PET drug CGMP requirements and approval procedures.

We presented our initial tentative approach to PET drug CGMP requirements and responded to numerous questions and comments about that approach at a public meeting on February 19, 1999. In the **Federal Register** of September 22, 1999 (64 FR 51274), we published a notice of availability of preliminary draft regulations on PET drug CGMP. Those preliminary draft regulations were discussed at a public meeting on September 28, 1999.

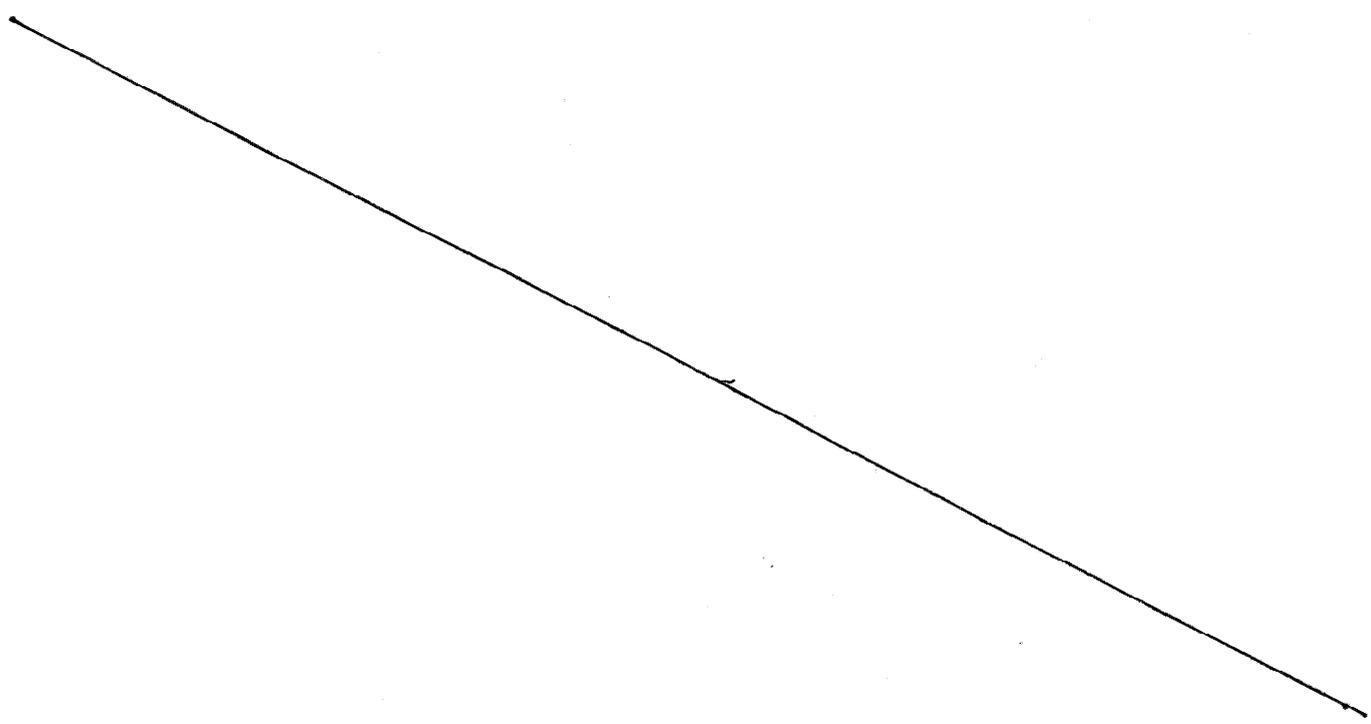
After considering the comments on the preliminary draft regulations, FDA has decided to make several revisions to its approach to CGMP for PET drug products. In accordance with 21 CFR 10.40(f)(4) and 10.80(b)(2), we are making revised preliminary draft regulations available for comment. The preliminary draft proposed rule does not include sections on the economic impact of the proposed rule, federalism concerns, and Paperwork Reduction Act issues. We will include

these sections when we publish a proposed rule, but we invite comments on these matters at this time.

Elsewhere in this issue of the **Federal Register**, we are announcing the availability of a companion draft guidance entitled "PET Drug Products—Current Good Manufacturing Practice (CGMP)." Both the preliminary draft proposed rule and the draft guidance will be discussed at a public meeting to be held on May 21, 2002, from 9 a.m. to 4:30 p.m., at 5630 Fishers Lane, rm. 1066, Rockville, MD 20852.

II. Comments

Interested persons may submit to the Dockets Management Branch (address above) written or electronic comments on the preliminary draft proposed rule. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Electronic comments may be submitted to <http://www.fda.gov/dockets/ecomments>. The preliminary draft proposed rule and the comments submitted to this docket may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

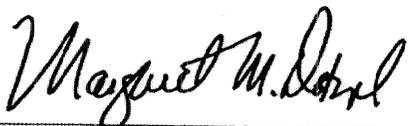


III. Electronic Access

Persons with access to the Internet may obtain the document at <http://www.fda.gov/ohrms/dockets/default.htm> or www.fda.gov/cder/fdama under "Section 121—PET (Positron Emission Tomography)."

(Authority: 21 U.S.C. 321 *et seq.*)

Dated: March 25, 2002



Margaret M. Dotzel,
Associate Commissioner for Policy.

[FR Doc. 02-????? Filed ??-??-02; 8:45 am]

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PRELIMINARY DRAFT

**CURRENT GOOD MANUFACTURING PRACTICE FOR POSITRON
EMISSION TOMOGRAPHY DRUGS**

Preliminary Draft Proposed Rule

Submit comments on this preliminary draft proposed rule on or before June 5, 2002. Submit written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to <http://www.fda.gov/dockets/comments>. All comments should be identified with the docket number listed in the notice of availability that is published in the *Federal Register*.

Table of Contents

- I. Introduction
 - A. Background

PRELIMINARY DRAFT

- B. The Nature of PET Drug Production and Our Proposed Regulations
- II. Description of the Preliminary Draft Proposed Rule
- A. Exclusion of PET Drug Products from CGMP Regulations in Parts 210 and 211
 - B. Definitions
 - C. Describing CGMP Requirements for PET Drugs
 - D. Adequate Personnel and Resources
 - E. Quality Control System
 - F. Facilities and Equipment
 - G. Control of Components, Containers, and Closures
 - H. Production and Process Controls
 - I. Laboratory Testing Requirements
 - J. Stability
 - K. Controls and Acceptance Criteria for Finished Products
 - L. Actions To Be Taken if Product Does Not Conform to Specifications
 - M. Labeling and Packaging
 - N. Distribution Controls
 - O. Complaint Handling
 - P. Records
- III. Analysis of Economic Impacts [to be added later]
- IV. Environmental Impact

PRELIMINARY DRAFT

- V. The Paperwork Reduction Act of 1995 [to be added later]
- VI. Federalism [to be added later]
- VII. Proposed Effective Date
- VIII. Request for Comments

PRELIMINARY DRAFT

Introduction

A. Background

Positron emission tomography is a medical imaging modality involving the use of a unique type of radiopharmaceutical drug product. The majority of PET drug products are injected intravenously into patients for diagnostic purposes. Most PET drugs are produced using cyclotrons and other production equipment at locations that are close to the patients to whom the drugs are administered (e.g., in hospitals or academic institutions). Due to their short half-lives, PET drugs usually are administered to patients within a few minutes or hours of production.

Under section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 351(a)(2)(B)), a drug is adulterated if the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to ensure that the drug meets the requirements of the act as to safety and has the identity and strength, and meets the quality and purity characteristics, that it purports or is represented to possess. Our CGMP requirements for non-PET drug products are set forth in parts 210 and 211 (21 CFR parts 210 and 211).

PRELIMINARY DRAFT

On November 21, 1997, the President signed the Food and Drug Administration Modernization Act of 1997 (Public Law 105-115) (the Modernization Act) into law. Section 121 of the Modernization Act contains several provisions affecting the regulation of PET drugs. Section 121(d)(1) directed us to terminate the application of a notice, published in the February 25, 1995, issue of the Federal Register (60 FR 10594), entitled "Regulation of Positron Emission Tomography Radiopharmaceutical Drug Products; Guidance; Public Workshop." That notice stated that traditional CGMP requirements in parts 210 and 211 were applicable to PET drugs. Section 121(d)(2) of the Modernization Act directed us to terminate the application of a notice that announced the availability of a draft guideline on the production of PET drugs (60 FR 10593, February 27, 1995). Section 121(d)(3) directed us to terminate the application of a final rule authorizing us to approve exceptions or alternatives to the application of CGMP requirements to the production of PET drugs (62 FR 19493, April 22, 1997). We terminated the application of these three documents in a notice (62 FR 66636) and final rule (62 FR 66522) published in the December 19, 1997, issue of the Federal Register.

Section 121(c)(1)(A) of the Modernization Act directs us to establish appropriate approval procedures and CGMP requirements

PRELIMINARY DRAFT

for PET drugs. Section 121(c)(1)(B) states that, in adopting such requirements, we must take due account of any relevant differences between not-for-profit institutions that compound PET drugs for their patients and commercial manufacturers of such drugs. Section 121(c)(1)(B) also directs us, as we develop PET drug CGMP requirements and approval procedures, to consult with patient advocacy groups, professional associations, manufacturers, and physicians and scientists who make or use PET drugs.

We presented our initial tentative approach to PET drug CGMP requirements and responded to numerous questions and comments about that approach at a public meeting on February 19, 1999. In the September 21, 1999, issue of the Federal Register (64 FR 51274), we published a notice of availability of preliminary draft regulations on PET drug CGMP requirements. These preliminary draft regulations were discussed at a public meeting on September 28, 1999. After considering the comments on the preliminary draft regulations, FDA has decided to make several changes to those regulations that are reflected in this preliminary draft proposed rule. After another public meeting, we intend to evaluate the comments, make appropriate changes, and publish a proposed rule for comment.

B. The Nature of PET Drug Production and Our Proposed

PRELIMINARY DRAFT

Regulations

As directed by Congress in the Modernization Act, to aid our development of these proposed regulations, we closely examined the operations of many PET drug producers, including not-for-profit institutions and commercial manufacturers. Since the Modernization Act became law, PET drug production in the United States has significantly changed. 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 have been produced by academicians and researchers at PET centers located in universities and similar not-for-profit institutions. Academically oriented PET centers usually produce small amounts (a few doses per day) of a few PET drug products for onsite 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 onsite, although often there is some distribution to other local or regional hospitals.

PRELIMINARY DRAFT

In addition, there are a growing number of independent PET centers that are not affiliated with any university or hospital. Typically these are for-profit, independently operated PET centers, though they are often contractually managed. These centers generally focus on producing one or two PET drug products and distribute them 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 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.

This preliminary draft proposed rule on CGMP requirements contains the minimum standards 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,

PRELIMINARY DRAFT

academically oriented institutions that make PET drug products for their own patients and research as well as larger commercial producers that serve a greater number of patients in a broader region.

In consideration of the unique nature of PET drugs and PET drug production, the proposed CGMP requirements for PET drug products differ from the requirements for non-PET drug products in many significant ways. These differences include the following:

1. Fewer required personnel with fewer organizational restrictions consistent with the scope and complexity of operations;
2. Allowance for multiple operations (or storage) in the same area as long organization and other controls are adequate;
3. Streamlined requirements for aseptic processing consistent with the nature of the production process;
4. Streamlined quality control requirements for components;
5. Self-verification of significant steps in PET drug production consistent with the scope and complexity of operations;
6. Same-person oversight of production, review of batch records, and authorization of product release consistent with the scope and complexity of operations;

PRELIMINARY DRAFT

7. Specialized quality control requirements for PET drugs produced in multiple sub-batches; and

8. Simplified labeling requirements consistent with the scope and complexity of operations.

These and other proposed PET CGMP provisions, designed to reflect the unique characteristics of PET drug production, should make it easier for PET centers to achieve compliance with CGMP requirements.

To further assist PET centers in complying with the requirements in the proposed rule, we are developing a companion draft guidance document entitled "PET Drug Products--Current Good Manufacturing Practice (CGMP)." For many aspects of CGMP (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 can use to comply with the CGMP requirements. We are specifically requesting comment on whether such a companion guidance would be a useful accompaniment to the proposed rule.

This preliminary draft proposed rule also incorporates principles from General Chapter <823>, "Radiopharmaceuticals for Positron Emission Tomography - Compounding," of the United States

PRELIMINARY DRAFT

Pharmacopeia (USP). The USP contains standards that are of significant regulatory importance for PET drugs. Under section 501(a)(2)(C) of the act, a compounded PET drug is adulterated unless it is produced in compliance with the USP's PET drug compounding standards and the official monograph for the particular PET drug. Section 121(b) of the Modernization Act added this provision as a safety net while we develop this rule. Under section 121(b), however, section 501(a)(2)(C) of the act will expire 2 years after the date on which we establish final approval procedures and CGMP requirements for PET drugs. At that time, compliance with the final version of this rule 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 these proposed CGMP requirements.

II. Description of the Preliminary Draft Proposed Rule

We are proposing to establish CGMP regulations for PET drug products by creating 21 CFR part 212. These regulations are intended to ensure that every PET drug product meets the requirements of the act as to safety and has the identity and strength, and meets the quality and purity characteristics, that

PRELIMINARY DRAFT

it is represented to possess.

Following is a section-by-section discussion of our preliminary draft CGMP regulations for PET drug products. The format of the preliminary draft regulations, including the use of questions in section headings, is in accordance with the Presidential Memorandum of June 1, 1998, promoting the use of "plain language" in regulatory writing.

A. Exclusion of PET Drug Products from CGMP Regulations in Parts 210 and 211

The preliminary draft proposed rule revises certain sections of parts 210 (CGMP for the manufacturing, processing, packing, or holding of drugs) and 211 (CGMP for finished pharmaceuticals) to make clear that the regulations in those parts do not apply to PET drug products. The revisions are in § 210.1 (status of CGMP regulations), § 210.2 (applicability of CGMP regulations), and § 210.3 (definitions). We propose revising the text of each of these sections so that the provisions will only apply to parts 210, 211, 225, and 226, rather than part 210 and parts 211 through 226. The revisions would exclude part 212, which will address PET drug products, from the scope of §§ 210.1, 210.2, and 210.3. Similarly, we propose to revise § 211.1(a) (scope of CGMP for finished pharmaceuticals) to clarify that the regulations in part 211 do not apply to PET drug products.

PRELIMINARY DRAFT

B. Definitions

Preliminary draft proposed § 212.1 sets forth the meaning of several terms used in the PET drug CGMP regulations. Most of the definitions are self-explanatory and well understood by PET producers and the pharmaceutical industry. We will discuss here a few of the definitions for which added comment may help the reader better understand the provision.

We propose to define "acceptance criteria" as numerical limits, ranges, or other criteria for tests that are used for or in making a decision to accept or reject a unit, lot, or batch of a PET drug product. This varies slightly from the definition in part 210, which states that acceptance criteria are the "product specifications and acceptance/rejection criteria, such as acceptable quality level and unacceptable quality level, with an associated sampling plan, that are necessary for making a decision to accept or reject a lot or batch (or any other convenient subgroups of manufactured units)." The proposed definition is more appropriate for PET drug production. We propose a separate definition of "specifications" to mean the tests, analytical procedures, and appropriate acceptance criteria that establish the criteria to which a PET drug, PET drug product, component, container closure system, in-process material, or other material used in PET drug production must

PRELIMINARY DRAFT

conform to be considered acceptable for its intended use. Conformance to specifications would mean that a PET drug, PET drug product, component, container closure system, in-process material, or other material used in PET drug production, when tested according to the described analytical procedures, meets the listed acceptance criteria. The definitions for acceptance criteria and specifications are designed to be consistent with International Conference on Harmonization guidance.

We propose to define "active pharmaceutical ingredient" (API) as a substance that is intended for incorporation into a finished PET drug product and is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the human body, excluding any intermediates used in the synthesis of such substance. For example, in the case of FDG F 18 injection drug product, 2-deoxy-2-[18F]fluoro-D-glucose is considered the API. In a commonly used production method for FDG F 18 injection, 1,3,4,6-tetra-O-acetyl-2-O-trifluoromethane sulfonyl- α -D-mannopyranose (mannose triflate) and O 18 water, obtained from a vendor, are considered components that yield the API but are not part of the API.

We propose to define "PET drug product" as a finished dosage form that contains a PET drug, whether or not in association with

PRELIMINARY DRAFT

one or more other ingredients. In other words, a PET drug product is the finished dosage form of a PET drug, with or without a diluent.

We propose to define "receiving facility" as any PET center, hospital, institution, imaging facility, other entity, or part of such an entity that accepts a PET drug product for human use. A receiving facility may be in the same area as or adjacent to the production area, in a different area but located in the same building as the production area, or at a site that is completely separate from the production area.

Proposed § 212.1 defines "material release" as the authoritative decision to permit the use of a component, container and closure, in-process material, packaging material, or labeling in the production of a PET drug product. "Final release," in contrast, is defined as the authoritative decision to permit the use of a batch of PET drug product in humans.

We propose to define "strength" as the concentration of the API (radioactivity amount per volume at the time of initial assay). This varies from the definition of "strength" in part 210 in that it specifies a radioactivity/volume ratio rather than a weight/weight, weight/volume, or unit dose/volume ratio. This definition of strength reflects that PET drug products have radioactive APIs (quantified in units of radioactivity) and

PRELIMINARY DRAFT

generally are produced in a solution or gas dosage form.

C. Describing CGMP Requirements for PET Drugs

Preliminary draft proposed § 212.2 answers the question "What is current good manufacturing practice for PET drugs?" Proposed § 212.2(a) describes CGMP for PET drug products as the minimum requirements for the methods to be used in, and the facilities and controls used for, the production, quality control, holding, or distribution of PET drug products intended for human use. The provision further states that the regulations in part 212 apply only to the manufacture or production of PET drug products. Any human drug product that does not meet the definition of a PET drug product must be manufactured in accordance with the CGMP requirements in parts 210 and 211.

Proposed § 212.2(b) specifies the matters that must be addressed in CGMP for PET drugs to ensure that each PET drug product meets the requirements of the act as to safety and has the identity and strength, and meets the quality and purity characteristics, that it is supposed to have. These matters are as follows:

1. Personnel and resources;
2. Quality control systems;
3. Facilities and equipment;
4. Control of components, in-process materials, and

PRELIMINARY DRAFT

finished products;

5. Production and process controls;
6. Laboratory controls;
7. Acceptance criteria;
8. Labeling and packaging controls;
9. Distribution controls;
10. Complaint handling; and
11. Record keeping.

D. Adequate Personnel and Resources

Preliminary draft proposed § 212.10 answers the question "What personnel and resources must I have?" Adequate personnel and resources would mean a sufficient number of personnel with the necessary education, background, training, and experience to enable them to perform their assigned functions, and adequate resources, including facilities and equipment, to enable them to perform their functions. What constitutes "adequate" personnel and resources will depend in part on the size and complexity of the PET drug producer's operations. A PET center having a simple operation that produces only one or two doses each day (or week) of a single PET drug would need fewer personnel and other resources than a PET center having a more complex operation that produces multiple PET drug products or a PET center producing larger amounts of a PET drug product.

PRELIMINARY DRAFT

E. Quality Control System

Preliminary draft proposed § 212.20 answers the question "What type of quality control system must I have?" Under proposed § 212.20(a), PET drug product producers must have a quality control unit that has the responsibility and authority to oversee production operations to ensure that each PET drug product meets the requirements of the act as to safety and has the identity and strength, and meets the quality and purity characteristics, that it is supposed to have. Each PET drug producer will determine what personnel should staff the quality control unit; at some PET centers, it may be reasonable for the same personnel to be involved in both production and quality control. Under proposed § 212.20(b), the quality control unit must examine and approve or reject components, containers, closures, in-process materials, packaging materials, labeling, and finished dosage forms to ensure compliance with procedures and specifications affecting the identity, strength, quality, or purity of a PET drug product.

Proposed § 212.20(c) states that the quality control unit must approve or reject specifications, methods, processes, or procedures, and any proposed changes to these that may affect the identity, strength, quality, or purity of a PET drug product before they are implemented. The quality control unit also must

PRELIMINARY DRAFT

assess the need for revalidation after there has been a change in specifications, methods, processes, or procedures.

Under proposed § 212.20(d), the quality control unit must review production records to determine whether errors have occurred. Possible errors include miscalculating yield, omitting a production step, or transcription mistakes. If errors have occurred or a production batch or its components fails to meet any of its specifications, the quality control unit must ensure that the errors or failures have been fully investigated and corrective action has been taken.

To ensure that the responsibilities of the quality control unit are known to all personnel involved in PET drug product production, proposed § 212.20(e) requires that the responsibilities of the unit and its operational procedures be in writing and followed.

F. Facilities and Equipment

Preliminary draft proposed § 212.30 answers the question "What requirements must my facilities and equipment meet?" Under proposed § 212.30(a), a PET drug producer must provide 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 that could reasonably be expected to

PRELIMINARY DRAFT

have an adverse effect on product quality. Proposed § 212.30(b) requires PET drug producers to implement procedures to ensure that all equipment that could reasonably be expected to adversely affect the strength, quality, or purity of a PET drug product (e.g., laminar airflow workbench, sterilizing filters) or give erroneous or invalid test results when improperly used or maintained (such as high pressure liquid chromatography (HPLC) devices) is clean, suitable for its intended purposes, properly installed, maintained, and capable of repeatedly producing valid results. PET centers must document their activities in accordance with these procedures. Proposed § 212.30(c) requires that equipment be constructed and maintained so that surfaces that contact components, in-process materials, or PET drug products are not reactive, additive, or absorptive so as to alter the quality of PET drug products.

G. Control of Components, Containers, and Closures

Preliminary draft proposed § 212.40 answers the question "How must I control the components I use to produce PET drugs and the containers and closures I package them in?" Under proposed § 212.40(a), PET drug producers must establish, maintain, and follow written procedures describing the receipt, log-in, identification, storage, handling, testing, approval, and rejection of components and drug product containers and closures.

PRELIMINARY DRAFT

The procedures must be adequate to ensure that the components, containers, and closures are suitable for their intended use. Proposed § 212.40(b) requires that PET drug producers establish appropriate written specifications for the identity, quality, and purity of components and for the identity and quality of drug product containers and closures.

Proposed § 212.40(c) specifies that, upon receipt, each lot of components and containers and closures must be uniquely identified and examined to determine whether it complies with the PET center's specifications. PET centers must not use in production any lot that does not meet its specifications, including any expiration date if applicable, or that has not yet received its material release. Any incoming lot must be appropriately designated as either quarantined, approved, or rejected.

Proposed § 212.40(c)(1) states that identity testing, using specific tests when available, must be conducted on each lot of a component that yields an API and each lot of an inactive ingredient. For example, in the case of FDG F 18 injection production, a PET center could use a reaction-based identity test for O 18 water involving the production of F 18 by nuclear bombardment. Alternatively, it could establish the identity of O 18 water by mass spectroscopy technique. To identify mannose

PRELIMINARY DRAFT

triflate, a PET center could use infrared spectroscopy or nuclear magnetic spectroscopy.

Proposed § 212.40(c)(1) also creates an exception to this requirement: If a PET center uses as an inactive ingredient a product that is marketed as a finished drug product intended for intravenous administration, there is no need to perform a specific identity test on the inactive ingredient. However, if an inactive ingredient (e.g., 0.9% sodium chloride solution) is prepared on site, the PET center must perform an identity test on the components used to make the inactive ingredient before the components are released for use. In such a case, the PET center should prepare the inactive ingredient in accordance with process controls in proposed § 212.50.

Identity testing of reagents and solvents is recommended but not required because the current nature of PET drug production (involving the use of small amounts of solvents and their removal during microscale chemical synthesis) makes it unlikely that any unintended toxic material such as organic solvents will be present in the finished drug product. If PET centers develop PET drugs that are more likely to contain toxic materials, identity testing should be performed, and we may need to propose an amendment to the regulations to address that concern.

Proposed § 212.40(c)(2) states that, in addition to identity

PRELIMINARY DRAFT

testing, a PET center must test a representative sample of each lot of a component, including components that yield an API and inactive ingredients, for conformity with its other written specifications. In place of such testing, the PET center may accept a lot of a component on the basis of a report of analysis on that lot from the supplier provided that the PET center has previously established the reliability of the supplier's test results.

Proposed § 212.40(c)(3) states that a representative sample of each lot of containers and closures must be examined for conformity to its written specifications. This should include an examination of the report of analysis. The PET center must perform at least a visual identification of each lot of containers and closures.

Proposed § 212.40(d) requires that components, containers, and closures be handled and stored in a manner that prevents contamination, mix-ups, and deterioration and ensures that these items are and remain suitable for their intended use. Under proposed § 212.40(e), PET drug producers must keep a record of each shipment of each lot of components, containers, and closures they receive. The record must include the identity and quantity of each shipment, the supplier's name and lot number, the date of receipt, the results of any testing performed, the disposition of

PRELIMINARY DRAFT

rejected material, and the expiration date.

H. Production and Process Controls

Preliminary draft proposed § 212.50 answers the question "What production and process controls must I have?" Proposed § 212.50 states that PET drug producers must have adequate production and process controls to ensure the consistent production of a PET drug product that meets the applicable standards of identity, strength, quality, and purity.

Under proposed § 212.50(a), PET drug producers must 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) requires PET drug producers to have a master production and control record that documents all steps in the PET drug product production process. The master production and control record must include the following:

1. The name and strength of the PET drug product;
2. If applicable, the name and weight or measurement of each API per batch or per unit of weight or measurement of the drug product, and a statement of the total weight or measurement of any dosage unit;
3. A complete list of components designated by names and codes sufficiently specific to indicate any special quality

PRELIMINARY DRAFT

characteristic;

4. Identification of all major pieces of equipment used in production;

5. An accurate statement of the weight or measurement of each component, using the same weight system (metric, avoirdupois, or apothecary) for each component (with reasonable variations permitted in the amount of component necessary if justified in the master production and control record);

6. A statement of action limits on radiochemical yield, i.e., the maximum and minimum percentages of yield beyond which investigation and corrective action are required;

7. Complete production and control instructions, sampling and testing procedures, specifications, special notations, and precautions to be followed; and

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

We are proposing to require a statement of action limits on radiochemical yield, rather than a statement of theoretical yield as appeared in § 212.50(c)(5) of the September 21, 1999, preliminary draft regulations. We agree with several comments that the term theoretical yield is inappropriate for describing the radiochemical synthesis of PET drug products because the

PRELIMINARY DRAFT

radiochemicals are measured in terms of radioactivity and are not weighed. The term radiochemical yield is more appropriate in this context. An anticipated radiochemical yield (within the established action limits) helps ensure that the process proceeded as expected; an abnormal radiochemical yield (lower or higher than expected) indicates that the process did not proceed as expected.

Proposed § 212.50(c) requires the creation of a unique batch and production control record each time a batch of a PET drug product is produced. The batch production record must include the following information: An identification number or other unique identifier of the specific batch that was produced, each production step (obtained from the approved appropriate master production and control record), weights and identification codes of components, dates of production steps, identification of major pieces of equipment, testing results, labeling, names (initials or signatures) of persons performing or checking each significant step in the operation, and results of any investigations conducted.

Under proposed § 212.50(d), the production area and all equipment therein must be checked to ensure cleanliness and suitability immediately before use, and a record of these checks must be kept.

PRELIMINARY DRAFT

Proposed § 212.50(e) specifies that process controls for PET centers must include control of in-process materials to ensure that the materials are controlled until required tests or other verification activities have been completed or necessary approvals are received and documented.

Under proposed § 212.50(f), the process for producing each PET drug product must be validated according to established procedures, and the quality control unit must approve both the validation process and the results of each validation activity. For example, the computer program used in the automated synthesis of FDG F 18 injection can be validated by demonstrating that acceptable production criteria for the drug product have been met for at least three consecutive production runs. Validation activities and results must be documented. Documentation must include the date and signature of the individual(s) approving the validation, the monitoring and control methods and data, and the major equipment validated.

For a PET center that has an established history of producing a particular PET drug product, validation of that production process may be conducted retrospectively provided that the process has not changed and has not resulted in process-related failures. However, prospective validation is required for any new production process and after any significant change

PRELIMINARY DRAFT

to a validated process.

I. Laboratory Testing Requirements

Preliminary draft proposed § 212.60 answers the question "What requirements apply to the laboratories where I test components, in-process materials, and finished PET drug products?" Under proposed § 212.60(a), each laboratory used to conduct testing of components, in-process materials, and finished PET drug products must have and follow written procedures for the conduct of each test and for the documentation of the results.

Proposed § 212.60(b) requires that each laboratory 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, including established standards of identity, strength, quality, and purity. Under proposed § 212.60(c), laboratory analytical methods must be suitable for their intended use and must be sufficiently sensitive, specific, accurate, and reproducible. If a compendial test is used, the testing laboratory should verify that the method works under the actual conditions of use and that the drug product as formulated can be analyzed using the compendial method. This verification is needed because many compendial methods for PET drug products lack specific information (e.g., do not describe specific equipment

PRELIMINARY DRAFT

used), the method may not have been developed in the context of the production method actually being used, and the PET center may not be using the same equipment that was used in the compendial method.

Proposed § 212.60(d) requires that the identity, purity, and quality of reagents, solutions, and supplies used in testing procedures be adequately controlled. All solutions prepared by the PET center must be properly labeled to show their identity, composition, and expiration date. Under proposed § 212.60(e), all equipment used to perform the testing must be suitable for its intended purposes and capable of producing valid results. Proposed § 212.60(f) requires that each laboratory have and follow written procedures to ensure that equipment is routinely calibrated, inspected, checked, and maintained, and that these activities be documented.

Under proposed § 212.60(g), each laboratory performing tests related to the production of a PET drug product must keep complete records of all tests performed to ensure compliance with established specifications and standards, including examinations and assays. These records must include the following:

1. A description of the sample received for testing, including its source, the quantity, the batch or lot number, the date and time the sample was taken, and the date and time the

PRELIMINARY DRAFT

sample was received for testing;

2. 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;

3. A complete record of all data obtained in the course of each test, including all graphs, charts, and spectra from laboratory instrumentation, properly identified to show the specific component, in-process material, or drug product for each lot tested;

4. A statement of the results of tests and how the results compare with established acceptance criteria; and

5. The initials or signature of the person performing the test and the date on which the test was performed.

J. Stability

Preliminary draft proposed § 212.61 answers the question "What must I do to ensure the stability of my PET drug products through expiry?" Under proposed § 212.61(a), PET centers must establish, follow, and maintain a written testing program to assess the stability characteristics of their PET drug products. The test methods must be reliable, meaningful, and specific. The samples tested must be representative of the lot or batch from which they were obtained and must be stored under suitable

PRELIMINARY DRAFT

conditions. Proposed § 212.61(b) requires that the results of the stability testing be documented and used in determining appropriate storage conditions and expiration dates and times for each PET drug product.

K. Controls and Acceptance Criteria for Finished Products

Preliminary draft proposed § 212.70 answers the question "What controls and acceptance criteria must I have for my finished PET drug products?" These controls and acceptance criteria are the requirements that must be met before a PET center may give final release to a finished PET drug product. Proposed § 212.70(a) states that PET centers must establish specifications for each batch of a PET drug product, including criteria for identity, strength, quality, purity, and, if appropriate, sterility and pyrogenicity. (Most, but not all, PET drugs are sterile injectable products, and for such products it is appropriate to have specifications for sterility and pyrogenicity.)

Proposed § 212.70(b) states that before a PET drug producer implements a test procedure in a specification, the producer must establish and document the accuracy, sensitivity, specificity, and reproducibility of the procedure.

Proposed § 212.70(c) directs PET drug producers to conduct laboratory testing of a representative sample of each batch of a

PRELIMINARY DRAFT

PET drug product to ensure that each product conforms to its specifications, except for sterility, before final release of the drug product. Producers must establish and document the accuracy, sensitivity, specificity, and reproducibility of the test methods. For a PET drug product produced in multiple sub-batches (e.g., ammonia N 13 injection), at least each initial sub-batch that is representative of the entire batch must conform to specifications, except for sterility, before final release.

Under proposed § 212.70(d), producers must establish and follow procedures to ensure that a PET drug product is not given final release until:

1. Appropriate laboratory testing under paragraph (a) of this section is completed,
2. Associated laboratory data and documentation are reviewed (review may be performed by a second person or self-verified in a one-person operation) and they demonstrate that the PET drug product meets specifications, except for sterility, and
3. A designated qualified individual (usually a person in the PET center's quality control unit) authorizes final release by dated signature.

In many cases, the short half-life of a PET radionuclide precludes the completion and review of all laboratory testing before release of the PET drug product for distribution to a

PRELIMINARY DRAFT

receiving facility. In such cases, release for distribution in accordance with previously established and documented procedures is acceptable as long as all testing and review, except for sterility, is completed before final release of the drug product (i.e., the decision by the quality control unit to permit the use of the product). The PET center should document the communication of this authoritative decision to the receiving facility.

Because of the short half-lives of PET radionuclides, under proposed § 212.70(e), sterility testing need not be completed before final release but must be started within 24 hours of sterile filtration (end of production). Product samples must be tested individually and must not be pooled. If the product fails the sterility test, all facilities that have received the product must be notified of the results immediately. The notification must include any appropriate recommendations and must be documented.

At the September 28, 1999, public meeting on PET drug product CGMP, some commenters suggested that the regulations allow PET centers to release a PET drug product if they experience an unanticipated, temporary failure of analytical equipment that prevents them from completing final release testing. The commenters maintained that having duplicative

PRELIMINARY DRAFT

equipment was difficult for smaller PET centers. They stated that having to cancel scheduled PET scans because of analytical equipment failure would inconvenience physicians and patients, some of whom may have traveled long distances to undergo the diagnostic procedure.

We are considering whether to include a provision in the CGMP regulations that would permit final release of a PET drug product even though the PET center could not complete a required finished product test because of equipment failure. However, we do not want to create an exception that would expose patients to unnecessary risks for the sake of convenience or that would encourage poor maintenance practices. Therefore, any such provision in the regulations would include certain conditions under which such release would be permitted. The PET drug producer could be required to meet the following conditions:

(1) Have documentation of previous successful use of a test that cannot be completed and evidence to show consistent performance by multiple batches meeting the specifications; (2) complete the omitted test using the reserve sample after the analytical equipment is repaired; and (3) notify the receiving facility in the case of an out-of-specification result.

To help us determine whether to propose this exemption from testing requirements, we are requesting comment on the following:

PRELIMINARY DRAFT

1. How frequently do breakdowns of analytical testing equipment occur?
2. What is the likelihood that an alternative testing method would be available?
3. If a PET drug product could not be released for administration to patients because laboratory testing could not be completed due to equipment failure, what is the likelihood that a different PET center could provide the appropriate PET drug product for these patients?
4. Should there be a specific regulation permitting final release of a PET drug product even though testing cannot be completed due to a failure of equipment?
5. If so, what conditions for release should be established to limit potential risk to patients and ensure that such release does not become standard practice?
6. Should the receiving facility be notified of the information that is unavailable because of the equipment failure?

We will consider any comments that we receive on these matters and determine how to address this issue in the proposed rule.

L. Actions To Be Taken if Product Does Not Conform to Specifications

Preliminary draft proposed § 212.71 answers the question

PRELIMINARY DRAFT

"What actions must I take if a batch of PET drug product does not conform to specifications?" Proposed § 212.71(a) states that if a batch of a PET drug product does not conform to specifications, the PET drug producer must reject it. The quality control unit must identify and segregate the product to avoid mix-ups. The PET center must have and follow procedures to investigate the cause(s) of the nonconforming product. The investigation must include, but should not be limited to, examination of processes, operations, records, complaints, and any other relevant sources of information concerning the nonconforming product.

Proposed § 212.71(b) requires PET centers to document the investigation of a PET drug product that does not conform to specifications. The documentation must include the results of the investigation and what happened to the rejected PET drug product. Under proposed § 212.71(c), PET centers must take action to correct any identified problems to prevent recurrence of a nonconforming product or other quality problem.

Under proposed 212.71(d), a PET center may reprocess a batch of a PET drug product that does not conform to specifications, if appropriate. If material that does not meet acceptance criteria is reprocessed, the producer must follow preestablished procedures (set forth in production and process controls) and the finished product must conform to specifications, except for

PRELIMINARY DRAFT

sterility, before final release.

M. Labeling and Packaging

Preliminary draft proposed § 212.80 answers the question "What are the requirements associated with labeling and packaging PET drug products? Under proposed § 212.80(a), a PET drug product must be suitably labeled and packaged to ensure that the integrity of the product is maintained during shipping.

Proposed § 212.80(b) states that labels must be legible and applied so as to remain legible and affixed during the established conditions of processing, storage, handling, distribution, and use. Proposed § 212.80(c) specifies that all information stated on each label must be contained in each batch production record.

Proposed § 212.80(d) requires that labeling and packaging operations be controlled to prevent product and labeling mix-ups.

Under proposed § 212.80(e), each PET drug producer must ensure that packaging and shipping containers for PET drug products are designed and constructed to protect against alteration or damage during the established conditions of storage, handling, distribution, and use.

N. Distribution Controls

Preliminary draft proposed § 212.90 answers the question "What actions must I take to control the distribution of PET drug

PRELIMINARY DRAFT

products?" This section would primarily apply to PET centers that distribute PET drug products beyond the immediate vicinity of the production site. In § 212.90(a), we propose that PET drug producers establish, maintain, and follow written procedures for the control of distribution of PET drug products shipped from the PET center to ensure that only those products approved for final release are used and that the process of shipping will not adversely affect the identity, purity, or quality of the PET drug product. Under proposed § 212.90(b), producers must maintain distribution records for each PET drug product that include or refer to the following:

1. The name, address, and telephone number of the receiving facility that received each batch of a PET drug product;
2. The name and quantity of the PET drug product shipped;
3. The lot number, control number, or batch number for the PET drug product shipped; and
4. The date and time the PET drug product was shipped.

O. Complaint Handling

Preliminary draft proposed § 212.100 answers the question "What do I do if I receive a complaint about a PET drug product produced at my facility?" Proposed § 212.100(a) directs PET drug producers to develop and follow written procedures for the receipt and handling of all complaints concerning a PET drug

PRELIMINARY DRAFT

product.

Proposed § 212.100(b) requires that the procedures include review by the quality control unit of any complaint involving the possible failure of a PET drug product to meet any of its specifications and investigation to determine the cause of the failure.

Under proposed § 212.100(c), producers must maintain a written record of each complaint in a file designated for PET drug product complaints. The record must include 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 complaint record must also include the findings of any investigation and follow-up.

Proposed § 212.100(d) states that a PET drug product that is returned because of a complaint may not be reprocessed and must be destroyed in accordance with applicable Federal and State law.

P. Records

Preliminary draft proposed § 212.110 answers the question "How must I maintain records of my production of PET drug products?" Under proposed § 212.110(a), PET drug producers must maintain all records at the PET center or another location that is reasonably accessible to responsible officials of the PET

PRELIMINARY DRAFT

center and to employees of FDA designated to perform inspections. A reasonably accessible location is one that would enable the PET center to make requested records available to us in a reasonable period of time. Records, including those not stored at the inspected establishment, must be legible, stored to prevent deterioration or loss, and readily available for review and copying by FDA employees. In proposed § 212.110(b), we are requiring that PET drug producers maintain all records and documentation referenced in other parts of this regulation for a period of at least 1 year from the date of final release of a PET drug product.

III. Analysis of Economic Impacts [to be added later]

IV. Environmental Impact

We have determined under 21 CFR 25.30(j) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

V. The Paperwork Reduction Act of 1995 [to be added later]

VI. Federalism [to be added later]

VII. Proposed Effective Date

In accordance with section 121 of the Modernization Act, we propose that any final rule that may issue based on this proposal

PRELIMINARY DRAFT

become effective 2 years after the date on which we issue the final rule.

VIII. Request for Comments

Interested persons may, on or before June 5, 2002, submit to the Dockets Management Branch (address above) written comments on this preliminary draft proposed rule. Two copies are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

List of Subjects

21 CFR Part 210

Drugs, Packaging and containers.

21 CFR Part 211

Drugs, Labeling, Laboratories, Packaging and containers, Prescription drugs, Reporting and recordkeeping requirements, Warehouses.

21 CFR Part 212

Current good manufacturing practices, Positron emission tomography drugs.

Under the Federal Food, Drug, and Cosmetic Act, the Food and Drug Modernization Act, and under authority delegated to the

PRELIMINARY DRAFT

Commissioner of Food and Drugs, it is proposed that 21 CFR chapter I be amended as follows:

PART 210--CURRENT GOOD MANUFACTURING PRACTICE IN MANUFACTURING, PROCESSING, PACKING, OR HOLDING OF DRUGS; GENERAL

1. The authority citation for 21 CFR part 210 continues to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 355, 360b, 371, 374.

§ 210.1 [Amended]

2. Amend § 210.1 Status of current good manufacturing practice regulations by removing the phrase "211 through 226" both times it appears and adding in its place the phrase "211, 225, and 226".

§ 210.2 [Amended]

3. Amend § 210.2 Applicability of current good manufacturing practice regulations by removing the phrase "211 through 226" both times it appears and by adding in its place the phrase "211, 225, and 226".

210.3 [Amended]

4. Amend § 210.3 Definitions in paragraph (b) by removing the phrase "211 through 226" and adding in its place the phrase "211, 225, and 226."

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PART 211--CURRENT GOOD MANUFACTURING PRACTICE FOR FINISHED

PRELIMINARY DRAFT

PHARMACEUTICALS

1. The authority citation for 21 CFR part 211 continues to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 355, 360b, 371, 374.

2. Amend § 211.1 by revising paragraph (a) to read as follows:

§ 211.1 Scope.

(a) The regulations in this part contain the minimum current good manufacturing practice for preparation of drug products (excluding positron emission tomography drug products) for administration to humans or animals.

* * * * *

7. Add part 212 to read as follows:

PART 212--CURRENT GOOD MANUFACTURING PRACTICES FOR POSITRON
EMISSION TOMOGRAPHY DRUGS

Subpart A--General Provisions

Sec.

212.1 What are the meanings of the technical terms used in these regulations?

212.2 What is current good manufacturing practice for PET drugs?

Subpart B--Personnel and Resources

212.10 What personnel and resources must I have?

Subpart C--Quality Control

PRELIMINARY DRAFT

212.20 What type of quality control system must I have?

Subpart D--Facilities and Equipment

212.30 What requirements must my facilities and equipment meet?

Subpart E--Control of Components, Containers, and Closures

212.40 How must I control the components I use to produce PET drugs and the containers and closures I package them in?

Subpart F--Production and Process Controls

212.50 What production and process controls must I have?

Subpart G--Laboratory Controls

212.60 What requirements apply to the laboratories where I test components, in-process materials, and finished PET drug products?

212.61 What must I do to ensure the stability of my PET drug products through expiry?

Subpart H--Finished Drug Product Controls and Acceptance Criteria

212.70 What controls and acceptance criteria must I have for my finished PET drug products?

212.71 What other actions must I take if a batch of PET drug product does not conform to specifications?

Subpart I--Packaging and Labeling

212.80 What are the requirements associated with labeling and packaging PET drug products?

Subpart J--Distribution

212.90 What actions must I take to control the distribution of

PRELIMINARY DRAFT

PET drug products?

Subpart K--Complaint Handling

212.100 What do I do if I receive a complaint about a PET drug product produced at my facility?

Subpart L--Records

212.110 How must I maintain records of my production of PET drug products?

Authority: 21 U.S.C. 321, 351, 352, 355, 371, 374.

Subpart A--General Provisions

§ 212.1 What are the meanings of the technical terms used in these regulations?

The following definitions apply to words and phrases as they are used in this part. Other definitions of these words may apply when they are used in other parts of this chapter.

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

Act means the Federal Food, Drug, and Cosmetic Act, as amended (21 U.S.C. 321 et seq.).

Active pharmaceutical ingredient means a substance that is intended for incorporation into a finished PET drug product and is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or

PRELIMINARY DRAFT

prevention of disease, or to affect the structure or any function of the human body, excluding intermediates used in the synthesis of such substance.

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

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

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

Inactive ingredient means any intended component of the drug product other than the active pharmaceutical ingredient.

Lot means a batch, or a specifically identified portion of a batch, having uniform character and quality within specified limits. In the case of a PET drug product produced by continuous process, a lot is a specifically identified amount produced in a unit of time or quantity in a manner that ensures its having uniform character and quality within specified limits.

Lot number, control number, or batch number means any distinctive combination of letters, numbers, or symbols, or any

PRELIMINARY DRAFT

combination of them, from which the complete history of the production, processing, packing, holding, and distribution of a batch or lot of a PET drug product, or target material used specifically in the preparation of a PET drug product, can be determined.

Master production and control record means a compilation of records containing the procedures and specifications for the production of a PET drug product.

Material release means the authoritative decision to permit the use of a component, container and closure, in-process material, packaging material, or labeling in the production of a PET drug product.

PET means positron emission tomography.

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

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

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

Production means the manufacturing, compounding, processing,

PRELIMINARY DRAFT

packaging, labeling, reprocessing, repacking, relabeling, and testing of a PET drug product.

Quality control means a system for maintaining the quality of active ingredients, PET drug products, intermediates, components that yield an active pharmaceutical ingredient, analytical supplies, and other components, including container-closure systems and in-process materials, through procedures, tests, analytical methods, and acceptance criteria.

Quality control unit means any person or organizational element designated by a PET center to be responsible for the duties relating to quality control.

Receiving facility means any PET center, hospital, institution, imaging facility, or other entity, or part of an entity that accepts a PET drug product for human use.

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

PRELIMINARY DRAFT

meets the listed acceptance criteria.

Strength means the concentration of the active pharmaceutical ingredient (radioactivity amount per volume at the time of initial assay).

Validation means establishment of a documented program providing a high degree of assurance that a specific method, process, or system will consistently produce a result that meets predetermined acceptance criteria.

Verification means confirmation that an established method, process, or system produces a result that meets predetermined acceptance criteria.

You means any person who engages in the activities related to production and/or distribution of a PET drug product for use in humans.

§ 212.2 What is current good manufacturing practice for PET drugs?

(a) Current good manufacturing practice for PET drug products is the minimum requirements for the methods to be used in, and the facilities and controls used for, the production, quality control, holding, or distribution of PET drug products intended for human use. The regulations in this part apply only to the manufacture or production of PET drug products. Any human drug product that does not meet the definition of a PET drug

PRELIMINARY DRAFT

product must be manufactured in accordance with the current good manufacturing practice requirements in parts 210 and 211.

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

- (i) Personnel and resources;
- (ii) Quality control systems;
- (iii) Facilities and equipment;
- (iv) Control of components, in-process materials, and finished products;
- (v) Production and process controls;
- (vi) Laboratory controls;
- (vii) Acceptance criteria;
- (viii) Labeling and packaging controls;
- (ix) Distribution controls;
- (x) Complaint handling; and
- (xi) Record keeping.

Subpart B--Personnel and Resources

§ 212.10 What personnel and resources must I have?

You must have a sufficient number of personnel with the necessary education, background, training, and experience to

PRELIMINARY DRAFT

perform their assigned functions. You must have adequate resources, including facilities and equipment, to enable your personnel to perform their functions.

Subpart C--Quality Control

§ 212.20 What type of quality control system must I have?

(a) You must have a quality control unit that has the responsibility and authority to oversee production operations to ensure that each PET drug product meets the requirements of the act as to safety and has the identity and strength, and meets the quality and purity characteristics, that it is supposed to have.

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

(c) The quality control unit must approve or reject specifications, methods, processes, or procedures, and any proposed changes to these that may affect the identity, strength, quality, or purity of a PET drug product before they are implemented. The unit also must assess the need for revalidation after there has been a change in specifications, methods, processes, or procedures.

(d) The quality control unit must review production records

PRELIMINARY DRAFT

to determine whether errors have occurred. If errors have occurred, or a production batch or its components fails to meet any of its specifications, the quality control unit must ensure that the errors or failures have been fully investigated and corrective action has been taken.

(e) To ensure that the responsibilities of the quality control unit are known to all personnel involved in the production of PET drug products, the responsibilities of the unit and its operational procedures must be in writing and followed.

Subpart D--Facilities and Equipment

§ 212.30 What requirements must my facilities and equipment meet?

(a) You must provide 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 that could reasonably be expected to have an adverse effect on product quality.

(b) You must implement procedures to ensure that all equipment that could reasonably be expected to adversely affect the identity, strength, quality, or purity of a PET drug product, or give erroneous or invalid test results when improperly used or maintained, is clean, suitable for its intended purposes,

PRELIMINARY DRAFT

properly installed, maintained, and capable of repeatedly producing valid results. You must document your activities in accordance with these procedures.

(c) Equipment must be constructed and maintained so that surfaces that contact components, in-process materials, or PET drug products are not reactive, additive, or absorptive so as to alter the quality of PET drug products.

Subpart E--Control of Components, Containers, and Closures

§ 212.40 How must I control the components I use to produce PET drugs and the containers and closures I package them in?

(a) Written procedures. You must establish, maintain, and follow written procedures describing the receipt, log-in, identification, storage, handling, testing, and acceptance and/or rejection of components and drug product containers and closures. The procedures must be adequate to ensure that the components, containers, and closures are suitable for their intended use.

(b) Written specifications. You must establish appropriate written specifications for the identity, quality, and purity of components and for the identity and quality of drug product containers and closures.

(c) Examination and testing. Upon receipt, each lot of components and containers and closures must be uniquely identified and examined to determine whether the lot complies

PRELIMINARY DRAFT

with your specifications. You must not use in PET drug production any lot that does not meet its specifications, including any expiration date if applicable, or that has not yet received its material release. Any incoming lot must be appropriately designated as either quarantined, accepted, or rejected.

(1) You must conduct identity testing, using specific tests when available, on each lot of a component that yields an active pharmaceutical ingredient and each lot of an inactive ingredient. However, if you use as an inactive ingredient a product that is marketed as a finished drug product intended for intravenous administration, you need not perform a specific identity test on that ingredient. Conversely, if you prepare an inactive ingredient on site, you must perform an identity test on the components used to make the inactive ingredient before the components are released for use.

(2) In addition to identity testing, you must test a representative sample of each lot of a component, including components that yield an active pharmaceutical ingredient and inactive ingredients, to ensure conformity with its other written specifications. In place of such testing, you may accept a lot of a component on the basis of a report of analysis on that lot from the supplier provided that you have previously established

PRELIMINARY DRAFT

the reliability of the supplier's test results.

(3) You must examine a representative sample of each lot of containers and closures for conformity to its written specifications. You must perform at least a visual identification of each lot of containers and closures.

(d) Handling and storage. You must handle and store components, containers, and closures in a manner that prevents contamination, mix-ups, and deterioration and ensures that they are and remain suitable for their intended use.

(e) Records. You must keep a record for each shipment of each lot of components, containers, and closures that you receive. The record must include the identity and quantity of each shipment, the supplier's name and lot number, the date of receipt, the results of any testing performed, the disposition of rejected material, and the expiration date.

Subpart F--Production and Process Controls

§ 212.50 What production and process controls must I have?

You must have adequate production and process controls to ensure the consistent production of a PET drug product that meets the applicable standards of identity, strength, quality, and purity.

(a) Written control procedures. You must have written production and process control procedures to ensure and document

PRELIMINARY DRAFT

that all key process parameters are controlled and that any deviations from the procedures are justified.

(b) Master production and control record. You must have a master production and control record that documents all steps in the PET drug production process. The master production and control record must include:

- (1) The name and strength of the PET drug product;
- (2) If applicable, the name and weight or measurement of each active pharmaceutical ingredient per batch or per unit of weight or measurement of the drug product, and a statement of the total weight or measurement of any dosage unit;
- (3) A complete list of components designated by names and codes sufficiently specific to indicate any special quality characteristic;
- (4) Identification of all major pieces of equipment used in production;
- (5) An accurate statement of the weight or measurement of each component, using the same weight system (metric, avoirdupois, or apothecary) for each component. Reasonable variations are permitted in the amount of component necessary if they are justified in the master production and control record.
- (6) A statement of action limits on radiochemical yield, i.e., the maximum and minimum percentages of yield beyond which

PRELIMINARY DRAFT

investigation and corrective action are required;

(7) Complete production and control instructions, sampling and testing procedures, specifications, special notations, and precautions to be followed; and

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

(c) Batch production and control record. Each time a batch of a PET drug product is produced, a unique batch production and control record must be created. The batch production record must include the following information:

(1) Identification number or other unique identifier of the specific batch that was produced;

(2) Each production step (obtained from the approved appropriate master production and control record);

(3) Weights and identification codes of components;

(4) Dates of production steps;

(5) Identification of major pieces of equipment;

(6) Testing results;

(7) Labeling;

(8) Names (initials or signatures) of persons performing or checking each significant step in the operation; and

(9) Results of any investigations conducted.

PRELIMINARY DRAFT

(d) Area and equipment checks. The production area and all equipment therein must be checked to ensure cleanliness and suitability immediately before use. A record of these checks must be kept.

(e) In-process materials controls. Process controls must include control of in-process materials to ensure that the materials are controlled until required tests or other verification activities have been completed or necessary approvals are received and documented.

(f) Validation procedures. The process for producing each PET drug product must be validated according to established procedures, and the quality control unit must approve both the validation process and the results of each validation activity. Validation activities and results must be documented.

Documentation must include the date and signature of the individual(s) approving the validation, the monitoring and control methods and data, and the major equipment validated.

Subpart G--Laboratory Controls

§ 212.60 What requirements apply to the laboratories where I test components, in-process materials, and finished PET drug products?

(a) Testing procedures. Each laboratory used to conduct testing of components, in-process materials, and finished PET

PRELIMINARY DRAFT

drug products must have and follow written procedures for the conduct of each test and for the documentation of the results.

(b) Standards. Each laboratory must 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, including established standards of identity, strength, quality, and purity.

(c) Analytical methods. Laboratory analytical methods must be suitable for their intended use and must be sufficiently sensitive, specific, accurate, and reproducible.

(d) Materials. The identity, purity, and quality of reagents, solutions, and supplies used in testing procedures must be adequately controlled. All solutions that you prepare must be properly labeled to show their identity, composition, and expiration date.

(e) Equipment. All equipment used to perform the testing must be suitable for its intended purposes and capable of producing valid results.

(f) Equipment maintenance. Each laboratory must have and follow written procedures to ensure that equipment is routinely calibrated, inspected, checked, and maintained, and that these activities are documented.

(g) Test records. Each laboratory performing tests related

PRELIMINARY DRAFT

to the production of a PET drug product must keep complete records of all tests performed to ensure compliance with established specifications and standards, including examinations and assays, as follows:

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

(2) 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.

(3) A complete record of all data obtained in the course of each test, including all graphs, charts, and spectra from laboratory instrumentation, properly identified to show the specific component, in-process material, or drug product for each lot tested.

(4) A statement of the results of tests and how the results compare with established acceptance criteria.

(5) The initials or signature of the person performing the test and the date on which the test was performed.

§ 212.61 What must I do to ensure the stability of my PET drug products through expiry?

PRELIMINARY DRAFT

(a) You must establish, follow, and maintain a written testing program to assess the stability characteristics of your PET drug products. The test methods must be reliable, meaningful, and specific. The samples tested must be representative of the lot or batch from which they were obtained and must be stored under suitable conditions.

(b) The results of such stability testing must be documented and used in determining appropriate storage conditions and expiration dates and times for each PET drug product you produce.

Subpart H--Finished Drug Product Controls and Acceptance Criteria
§ 212.70 What controls and acceptance criteria must I have for my finished PET drug products?

(a) Specifications. You must establish specifications for each batch of a PET drug product, including criteria for determining identity, strength, quality, purity, and, if appropriate, sterility and pyrogenicity.

(b) Test procedures. Before you implement a test procedure in a specification, you must establish and document the accuracy, sensitivity, specificity, and reproducibility of the procedure.

(c) Conformance to specifications. You must conduct laboratory testing of a representative sample of each batch of a PET drug product to ensure that the product conforms to

PRELIMINARY DRAFT

specifications, except for sterility, before final release. For a PET drug product produced in sub-batches, at least each initial sub-batch that is representative of the entire batch must conform to specifications, except for sterility, before final release.

(d) Final release procedures. You must establish and follow procedures to ensure that a PET drug product is not given final release until:

(1) Appropriate laboratory testing under paragraph (a) of this section is completed;

(2) Associated laboratory data and documentation are reviewed and they demonstrate that the PET drug product meets specifications, except for sterility; and

(3) A designated qualified individual authorizes final release by dated signature.

(e) Sterility testing. Sterility testing need not be completed before final release but must be started within 24 hours of sterile filtration (end of production). Product samples must be tested individually and must not be pooled. If the product fails the sterility test, all receiving facilities must be notified of the results immediately. The notification must include any appropriate recommendations and must be documented.

§ 212.71 What actions must I take if a batch of PET drug product does not conform to specifications?

PRELIMINARY DRAFT

(a) You must reject a batch of a PET drug product that does not conform to specifications. The quality control unit must identify and segregate the product to avoid mix-ups. You must have and follow procedures to investigate the cause(s) of the nonconforming product. The investigation must include, but is not limited to, examination of processes, operations, records, complaints, and any other relevant sources of information concerning the nonconforming product.

(b) You must document the investigation of a PET drug product that does not meet specifications, including the results of the investigation and what happened to the rejected PET drug product.

(c) You must take action to correct any identified problems to prevent recurrence of a nonconforming product or other quality problem.

(d) If appropriate, you may reprocess a batch of a PET drug product that does not conform to specifications. If material that does not meet acceptance criteria is reprocessed, you must follow preestablished procedures (set forth in production and process controls) and the finished product must conform to specifications before final release.

Subpart I--Packaging and Labeling

§ 212.80 What are the requirements associated with labeling and

PRELIMINARY DRAFT

packaging PET drug products?

(a) A PET drug product must be suitably labeled and packaged to ensure that the integrity of the product is maintained during shipping.

(b) Labels must be legible and applied so as to remain legible and affixed during the established conditions of processing, storage, handling, distribution, and use.

(c) All information stated on each label must be contained in each batch production record.

(d) Labeling and packaging operations must be controlled to prevent labeling and product mix-ups.

(e) You must ensure that packaging and shipping containers for PET drug products are designed and constructed to protect against alteration or damage during the established conditions of storage, handling, distribution, and use.

Subpart J--Distribution

§ 212.90 What actions must I take to control the distribution of PET drug products?

(a) You must establish, maintain, and follow written procedures for the control of distribution of PET drug products shipped from the PET center to ensure that only those products approved for final release are used and that the process of shipping will not adversely affect the identity, purity, or

PRELIMINARY DRAFT

quality of the PET drug product.

(b) You must maintain distribution records for each PET drug product that include or refer to the following:

(1) The name, address, and telephone number of the receiving facility that received each batch of a PET drug product;

(2) The name and quantity of the PET drug product shipped;

(3) The lot number, control number, or batch number for the PET drug product shipped; and

(4) The date and time you shipped the PET drug product.

Subpart K--Complaint Handling

§ 212.100 What do I do if I receive a complaint about a PET drug product produced at my facility?

(a) You must develop and follow written procedures for the receipt and handling of all complaints concerning a PET drug product.

(b) The procedures must include review by the quality control unit of any complaint involving the possible failure of a PET drug product to meet any of its specifications and investigation to determine the cause of the failure.

(c) A written record of each complaint must be maintained in a file designated for PET drug product complaints. The record must include the name and strength of the PET drug product, the

PRELIMINARY DRAFT

batch number, the name of the complainant, the date the complaint was received, the nature of the complaint, and the response to the complaint. It must also include the findings of any investigation and follow-up.

(d) A PET drug product that is returned because of a complaint may not be reprocessed and must be destroyed in accordance with applicable Federal and State law.

Subpart L--Records

§ 212.110 How must I maintain records of my production of PET drug products?

(a) Records must be maintained at the PET center or another location that is reasonably accessible to responsible officials of the PET center and to employees of FDA designated to perform inspections. All records, including those not stored at the inspected establishment, must be legible, stored to prevent deterioration or loss, and readily available for review and copying by FDA employees.

(b) You must maintain all records and documentation referenced in other parts of this regulation for a period of at least 1 year from the date of final release of a PET drug product.

Dated: _____
