§ 72.214 List of approved spent fuel storage casks.

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Certificate Number: 1004.

Initial Certificate Effective Date: January 23, 1995.

Amendment Number 1 Effective Date: April 27, 2000.

Amendment Number 2 Effective Date: September 5, 2000.

Amendment Number 3 Effective Date: September 12, 2001.

Amendment Number 4 Effective Date: February 12, 2002.

Amendment Number 5 Effective Date: January 7, 2004.

Amendment Number 6 Effective Date: December 22, 2003.

Amendment Number 7 Effective Date: March 2, 2004.

Amendment Number 8 Effective Date: December 5, 2005.

SAR Submitted by: Transnuclear, Inc.

SAR Title: Final Safety Analysis Report for the Standardized NUHOMS® Horizontal Modular Storage System for Irradiated Nuclear Fuel.

Docket Number: 72–1004.

Certificate Expiration Date: January 23, 2015.

Model Number: NUHOMS®–24P, –52B, –61BT, –32PT, –24PHB, and –24PTH.

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Dated at Rockville, Maryland, this 1st day of September, 2005.

For the Nuclear Regulatory Commission.

Luis A. Reyes,

Executive Director for Operations.

[FR Doc. 05–18663 Filed 9–19–05; 8:45 am]

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 210, 211, and 212

[Docket No. 2004N–0439]

Current Good Manufacturing Practice for Positron Emission Tomography Drugs

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing proposed regulations on current good manufacturing practice (CGMP) for positron emission tomography (PET) drug products. The regulations are intended to ensure that PET drug products meet the requirements of the Federal Food, Drug, and Cosmetic Act (the act) regarding safety, identity, strength, quality, and purity. We are proposing to establish CGMP requirements for approved PET drug products. For investigational and research PET drugs, the proposed rule states that the requirement to follow CGMP may be met by producing PET drugs in accordance with the United States Pharmacopeia (USP) general chapter on compounding PET radiopharmaceuticals. We are proposing to establish these CGMP requirements for all PET drugs under the provisions of the Food and Drug Administration Modernization Act of 1997 (the Modernization Act). Elsewhere in this issue of the **Federal Register**, FDA is announcing the availability of the draft guidance entitled ''PET Drug Products—Current Good Manufacturing Practice (CGMP).''

DATES: Submit written or electronic comments by December 19, 2005. Submit written comments on the information collection requirements by October 20, 2005. See section VII of this document for the proposed effective date of a final rule based on this document.

ADDRESSES: You may submit comments, identified by Docket No. 2004N–0439, by any of the following methods:

Electronic Submissions

Submit electronic comments in the following ways:

- Federal eRulemaking Portal: *http://www.regulations.gov*. Follow the instructions for submitting comments.
- Agency Web site: *http://www.fda.gov/dockets/ecomments*. Follow the instructions for submitting comments on the agency Web site.

Written Submissions

Submit written submissions in the following ways:

- FAX: 301–827–6870.
- Mail/Hand delivery/Courier [For paper, disk, or CD–ROM submissions]: Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

To ensure more timely processing of comments, FDA is no longer accepting comments submitted to the agency by e-mail. FDA encourages you to continue to submit electronic comments by using the Federal eRulemaking Portal or the agency Web site, as described in the Electronic Submissions portion of this paragraph.

Instructions: All submissions received must include the agency name and Docket No(s). or Regulatory Information Number (RIN) for this rulemaking. All comments received may be posted without change to *http://www.fda.gov/ohrms/dockets/default.htm*, including any personal information provided. For detailed instructions on submitting comments and additional information on the rulemaking process, see the ''Comments'' heading of the **SUPPLEMENTARY INFORMATION** section of this document.

Docket: For access to the docket to read background documents or comments received, go to *http://www.fda.gov/ohrms/dockets/default.htm* and insert the docket number(s), found in brackets in the heading of this document, into the ''Search'' box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Brenda Uratani, Center for Drug Evaluation and Research (HFD–320), Food and Drug Administration, 11919 Rockville Pike, Rockville, MD 20852, 301–827–8941.

SUPPLEMENTARY INFORMATION:

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I. 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 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 CGMP 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).

B. The Modernization Act and PET Drugs

On November 21, 1997, the President signed the Modernization Act (Public Law 105–115) into law. Section 121 of the Modernization Act contains several provisions affecting the regulation of PET drugs. Section 121(d) directed us to terminate the application of the following three **Federal Register** documents:

- A notice entitled ''Regulation of Positron Emission Tomography Radiopharmaceutical Drug Products; Guidance; Public Workshop'' (60 FR 10594, February 27, 1995). This notice stated that traditional CGMP requirements in parts 210 and 211 were applicable to PET drugs.
- A notice that announced the availability of a draft guideline on the production of PET drugs (60 FR 10593, February 27, 1995).
- 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 for PET drugs. Section 121(c)(2) of the Modernization Act provides that FDA cannot require the submission of a new drug application (NDA) or abbreviated new drug application (ANDA) for a PET drug product until 2 years after the day we publish a final rule establishing CGMP requirements for PET drug products.

Section 121(c)(1)(B) of the Modernization Act states that, in adopting CGMP and approval 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. We discuss the nature of PET drug production in section I.C of this document.

Section 121(c)(1)(B) of the Modernization Act 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 have taken the following steps in developing the PET drug CGMP regulations:

- 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 accordance with §§ 10.40(f)(4) and 10.80(b)(2) (21 CFR 10.40(f)(4) and 10.80(b)(2), we announced the availability of preliminary draft regulations on PET drug CGMP requirements in the September 22, 1999, issue of the **Federal Register** (64 FR 51274).
- We held a public meeting to discuss the preliminary draft regulations on September 28, 1999.
- After considering the comments on the preliminary draft regulations, in accordance with §§ 10.40(f)(4) and 10.80(b)(2), we announced the availability of a preliminary draft proposed rule on PET drug CGMP requirements in the April 1, 2002, issue of the **Federal Register** (67 FR 15344).
- We also announced the availability of a draft guidance on ''PET Drug Products—Current Good Manufacturing Practice for Positron Emission Tomography'' on April 1, 2002 (67 FR 15404).
- We held a public meeting to discuss the preliminary draft proposed rule and draft guidance on April 21, 2002.
- After considering the comments on the preliminary draft proposed rule, we are now issuing this proposed rule on PET drug CGMP requirements. Elsewhere in this issue of the **Federal Register**, we are making available for comment a revised draft guidance on CGMP for PET drug products.

C. The Nature of PET Drug Production and Our Proposed 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 production facilities has increased, as has the number of facilities where PET scans are performed. The business of PET drug production has changed as well. Historically, PET drug products were produced by academicians and researchers at facilities located in universities and similar not-for-profit institutions. These academically oriented PET production facilities 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 production facilities 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 there is some distribution to other local or regional hospitals.

In addition, there are a growing number of independent PET production facilities that are not affiliated with any university or hospital. Typically these are for-profit, independently operated facilities, although they are often contractually managed. These facilities 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 the following conclusions:

- 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 production facility needs to ensure product quality.
- Production and CGMP differences among PET drug producers are primarily a function of the size, scope, and complexity of their production operations.
- 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 facilities.

While this proposed rule and the draft guidance primarily reflect our familiarity with the current approved PET drugs (fludeoxyglucose (FDG) F 18 injection and ammonia N 13 injection), we intend both the proposed rule and the draft guidance to apply to future PET drug products. We also recognize that the development of new PET drug products may require us to amend regulations or guidance to accommodate the new products.

This proposed rule on CGMP requirements contains the minimum standards needed for PET drug production at all types of PET production facilities. We have designed the CGMP regulations to be sufficiently flexible to accommodate not-for-profit, academically oriented institutions as well as larger commercial producers.

In consideration of the unique nature of PET drugs and PET drug production, the proposed CGMP requirements for PET drug products differ in many significant ways from the CGMP requirements for non-PET drug products found in our regulations in part 211. The proposed PET CGMP requirements include the following differences:

- Fewer required personnel with fewer organizational restrictions consistent with the scope and complexity of operations;
- Allowance for multiple operations (or storage) in the same area as long as organization and other controls are adequate;
- Streamlined requirements for aseptic processing consistent with the nature of the production process;
- Streamlined quality control requirements for components;
- Self-verification of significant steps in PET drug production consistent with the scope and complexity of operations;
- Same-person oversight of production, review of batch records, and authorization of product release consistent with the scope and complexity of operations;
- Specialized quality control requirements for PET drugs produced in multiple sub-batches; and
- 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 production facilities to achieve compliance with CGMP requirements.

This proposed rule incorporates principles from Chapter <823>, ''Radiopharmaceuticals for Positron Emission Tomography—Compounding,'' of the 28th edition of the USP (2005) (USP 28). 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) of the Modernization Act, 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 28 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.

Moreover, as discussed in section II.D of this document, we believe that it is appropriate to designate the provisions of USP 28, Chapter <823> as the CGMP requirements for investigational PET drugs produced under an investigational new drug application (IND) and research PET drugs produced with the approval of a Radioactive Drug Research Committee (RDRC) under § 361.1 (21 CFR 361.1). Thus, under the proposed rule, investigational and research PET drugs produced in accordance with Chapter <823> would be deemed to meet CGMP requirements; they would not have to meet the more specific requirements in proposed part 212. Because most PET drugs currently are produced under an IND or RDRC review, adopting USP 28, Chapter <823> as the standard for CGMP for investigational PET drugs should make it easier for PET drug producers to comply with the proposed CGMP requirements.

To further assist PET production facilities in complying with the requirements in the rule, we have revised the 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 production facility's operations. The draft guidance provides practical examples of methods and procedures that different types of PET production facilities might use to comply with the CGMP requirements.

II. Description of the 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 it is represented to possess.

We describe our proposed CGMP regulations for PET drug production in the following sections of this document. The format of the proposed 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

We propose revising 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.

B. Definitions

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.

• *Acceptance criteria*. 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, which does not refer to sampling plans, is more appropriate for PET drug production.

• *Specifications*. We propose a separate definition of ''specifications'' to mean the tests, analytical procedures, and appropriate acceptance 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 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 intended to be consistent with guidance in ''Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products,'' prepared under the auspices of the International Conference on Harmonisation for Registration of Pharmaceuticals for Human Use (ICH). ICH works to promote the harmonization of technical requirements (including definitions, procedures, formats, and standards) for approval of pharmaceutical products among the European Union, Japan, and the United States.

• *Active pharmaceutical ingredient*. We propose to define ''active pharmaceutical ingredient'' (API) for purposes of part 212 as a substance (excluding intermediates used in the synthesis of such 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 or monitoring of a disease or a manifestation of a disease in humans. 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-β-D-mannopyranose (mannose triflate) and O 18 water are considered components that yield the API but are not part of the API.

• *PET drug*. We propose to define ''PET drug'' as a radioactive 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. The definition of PET drug includes any nonradioactive reagent, reagent kit, ingredient, nuclide generator, accelerator, target material, electronic synthesizer, or other apparatus or computer program to be used in the preparation of a PET drug. This definition closely parallels the statutory definition.

• *PET drug product*. We propose to define ''PET drug product'' as a finished dosage form that contains a PET drug, whether or not in association with one or more other ingredients. In other words, a PET drug product is the finished dosage form of a PET drug, with or without an excipient such as a diluent.

• *Receiving facility*. We propose to define ''receiving facility'' as any hospital, institution, nuclear pharmacy, imaging facility, or other entity or part of an entity that accepts a PET drug product that has been given final release. 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.

• *Material release and final release*. We propose to define ''material release'' as the authoritative decision by a responsible person in a PET production facility 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 by a responsible person in a PET production facility to permit the use of a batch of a PET drug product in humans.

• *Strength*. We propose to define ''strength'' as the concentration of the API (radioactivity amount per volume or weight at the time of calibration). This proposed definition varies from the definition of ''strength'' in part 210 in that it specifies a radioactivity to volume (or weight) ratio rather than a weight/weight, weight/volume, or unit dose/volume ratio. The definition of strength for proposed part 212 reflects that PET drug products have radioactive APIs (quantified in units of radioactivity) and generally are produced in a solution or gas dosage form.

C. Describing CGMP Requirements for PET Drugs

Proposed § 212.2 answers the question ''What is current good manufacturing practice for PET drugs?'' Proposed § 212.2 states that CGMP 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. CGMP is intended 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.

D. Applicability of CGMP Regulations

Proposed § 212.5 answers the question ''To what drugs do the regulations in this part apply?'' Proposed § 212.5(a) states that:

• Part 212 applies only to the production, quality control, holding, and distribution 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 of this chapter.

• Part 212 contains CGMP requirements for all PET drug products for human use, but proposed § 212.5(b) specifies different CGMP requirements for investigational and research PET drugs.

We believe that it is appropriate to have less detailed CGMP requirements for investigational and research PET drugs to allow for more flexibility in the production of these drugs. We also recognize that many investigational PET drugs may not have commercial potential. Therefore, proposed § 212.5(b) states that the regulations in part 212 do not apply to investigational PET drugs for human use produced under an IND in accordance with part 312 and research PET drugs produced with the approval of an RDRC in accordance with § 361.1. Instead, proposed § 212.5(b) states that, for investigational and research PET drugs, the requirement under the act to follow CGMP is met by producing drugs in accordance with USP 28 Chapter <823>, which is incorporated by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51. Chapter <823> sets forth requirements on several aspects of PET drug production, including control of components, materials, and supplies, verification of procedures, stability testing and expiration dating, quality control, and sterilization and sterility assurance. Because most PET drug producers are very familiar with the requirements in USP 28 Chapter <823>, adopting the Chapter <823> provisions as the CGMP requirements for investigational and research PET drugs should greatly facilitate producers' compliance with those requirements. Although the provisions in USP 28 Chapter <823>, including those on documentation, are generally less specific and explicit than the requirements in proposed part 212, we believe that they are adequate to ensure that investigational and research PET drugs are produced safely under appropriate conditions, consistent with section 501(a)(2)(B) of the act. We are interested in any comments that suggest appropriate standards, other than USP 28 Chapter <823>, for PET drugs and drug products produced under an IND or with the approval of an RDRC.

Although we propose that USP 28 Chapter <823>, rather than part 212, would constitute the minimum CGMP requirements for investigational and research PET drugs, FDA retains the authority under section 704 of the act (21 U.S.C. 374) to inspect facilities where investigational or research PET drugs are produced to verify compliance with USP 28 Chapter <823>. However, as with inspection of investigational studies of non-PET drugs, we generally would conduct inspections of facilities that produce investigational or research PET drugs only on a for-cause basis. An example of a situation that could lead to a for-cause inspection would be when we become aware of a potential safety concern related to the production of an investigational or research PET drug.

E. Adequate Personnel and Resources

Proposed § 212.10 answers the question ''What personnel and resources must I have?'' The proposal would require:

• A sufficient number of personnel with the necessary education, background, training, and experience to enable those personnel to perform their assigned functions, and

• Adequate resources, including facilities and equipment, to enable personnel 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 production facility 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 facility having a more complex operation that produces multiple PET drug products or a facility producing larger amounts of a PET drug product.

F. Quality Assurance

Proposed § 212.20 answers the question ''What activities must I perform to ensure product quality?'' Under proposed § 212.20, PET drug product producers would be required 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 (proposed § 212.20(a)). Each PET drug producer will determine what personnel should perform the quality assurance function; at some PET production facilities, it may be reasonable for the same personnel to be involved in both production and quality assurance.

• 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(b)).

• Approve or reject, before implementation, any initial specifications, methods, processes, or procedures, and any proposed changes to existing specifications, methods, processes, or procedures, to ensure that they maintain the identity, strength, quality, and purity of the PET drug product when they are implemented. PET drug producers must demonstrate that any change does not adversely affect the identity, strength, quality, or purity of any PET drug product (proposed § 212.20(c)).

• Review production records to determine whether errors have occurred. If errors have occurred or a production batch or any of its components fails to meet any of its specifications, the producer must determine the need for an investigation, conduct investigations when necessary, and take appropriate corrective action (proposed § 212.20(d)). Possible errors include miscalculating yield, omitting a production step, or transcription mistakes.

• Establish and follow written quality assurance procedures to ensure that quality assurance responsibilities are known to all personnel involved in PET drug product production (proposed § 212.20(e)).

G. Facilities and Equipment

Proposed § 212.30 answers the question ''What requirements must my facilities and equipment meet?'' Under proposed § 212.30, a PET drug producer would be required to:

• Provide adequate facilities to ensure the orderly handling of materials and equipment, the prevention of mixups, 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 (proposed § 212.30(a)).

• 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 (such as a laminar airflow workbench or 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 production facilities must document their activities in accordance with these procedures (proposed § 212.30(b)).

• Ensure that equipment is 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 (proposed § 212.30(c)).

H. Control of Components, Containers, and Closures

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, PET drug producers would be required to:

• Establish, maintain, and follow written procedures describing the receipt, login, identification, storage, handling, testing, approval, and 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 (proposed § 212.40(a)).

• 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(b)).

Proposed § 212.40(c) specifies that:

• Upon receipt, each lot of components and containers and closures must be uniquely identified and tested or examined to determine whether it complies with the PET production facility's specifications.

• Any lot that does not meet its specifications, including any expiration date if applicable, or that has not yet received its material release, must not be used in PET drug production.

• Any incoming lot must be appropriately designated as either quarantined, accepted, or rejected.

• PET drug producers must use a reliable supplier as a source of each lot of each component, container, and closure.

We are proposing to establish different requirements for examination and testing of components required under proposed § 212.40(c) depending on whether a PET drug producer conducts finished-product testing that includes testing to ensure that the correct components have been used:

• When the finished-product testing of a PET drug product includes testing to ensure that the correct components have been used, the PET drug producer need only determine that each lot of incoming components complies with written specifications by examining a certificate of analysis provided by the supplier (proposed § 212.40(c)(1)(i)). We believe that the use of this type of finished-product testing makes specific identity testing of components redundant and unnecessary. For example, when identity of the F 18 radionuclide is established as part of the finished-product testing and the method of production used is well-documented and understood (e.g., as in the ^{18}O (p,n) ^{18}F nuclear reaction), it can be reasonably argued that the component that yields this radionuclide is likely to be O 18 water. In this case, a specific identity test for O 18 water is not necessary before the lot is used in production. Similarly, a specific identity test before using a lot of mannose triflate may be redundant and unnecessary when: (1) A well-understood method of synthesis of FDG F 18 is used, (2) a test to confirm the radiochemical identity is performed in the finished drug product, and (3) the mannose triflate was obtained from a reliable supplier with whom a relationship has been previously established.

• If the finished-product testing of a PET drug product does not include testing to ensure that the correct components have been used, the following provisions (proposed § 212.40(c)(1)(ii)) would apply:

—The PET drug producer would be required to conduct identity testing, using a test that is specific to the component, on each lot of a component that yields an active ingredient and each lot of an inactive ingredient.

—For any other component, such as solvents or reagents, the PET drug producer would determine that each lot complies with written specifications by examining a certificate of analysis provided by the supplier.

—If the PET drug producer prepares an inactive ingredient on site, the producer would be required to perform an identity test on the components used to make the inactive ingredient before those components could be released for use.

However, if the PET drug producer uses as an inactive ingredient a product that is marketed as a finished drug product intended for intravenous administration, the producer would not need to perform a specific identity test on that ingredient.

We are also proposing that PET drug producers would be required to do the following:

• Examine a representative sample of each lot of containers and closures for conformity to its written specifications (proposed § 212.40(c)(2)).

• Perform at least a visual identification of each lot of containers and closures (proposed § 212.40(c)(2)).

• Handle and store components, containers, and closures in a manner that prevents contamination, mixups, and deterioration and ensures that these items are and remain suitable for their intended use (proposed § 212.40(d)).

• Keep a record of each shipment of each lot of components, containers, and closures they receive (proposed § 212.40(e)), including the following information:

—Identity and quantity of each shipment,

—Supplier's name and lot number,

—Date of receipt,

—Results of any testing performed,

—Disposition of rejected material, and

—Expiration date, where applicable. (Some components may not have expiration dates.)

I. Production and Process Controls

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. Proposed § 212.50 would require PET drug producers to have the following controls:

• Written production and process control procedures,

• Master production and control records,

• Batch and production control records,

• Production area and equipment checks,

• In-process materials controls, and

• Depending on finished-product testing, process verification.

The proposed written production and process control procedures would ensure and document that all key process parameters are controlled and that any deviations from the procedures are justified (proposed § 212.50(a)).

The proposed master production and control records would document all steps in the PET drug product production and would include the following information (proposed § 212.50(b)):

• The name and strength of the PET drug product;

• If applicable, the name and radioactivity or other measurement of each API and each inactive ingredient per batch or per unit of radioactivity or other measurement of the drug product, and a statement of the total radioactivity or other measurement of any dosage unit;

• A complete list of components designated by names and codes sufficiently specific to indicate any special quality characteristic;

• Identification of all major pieces of equipment used in production;

• 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 specified in the master production and control records);

• A statement of acceptance criteria on radiochemical yield, i.e., the minimum percentage of yield beyond which investigation and corrective action are required;

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

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

The creation of a unique batch and production control record would be required each time a batch of a PET drug product is produced (proposed § 212.50(c)), including the following information:

• The name and strength of the PET drug product,

• An identification number or other unique identifier of the specific batch that was produced,

• The name and radioactivity or other measure of each API and each inactive ingredient per batch or per unit of radioactivity or other measurement of the drug product,

• Each major production step (obtained from the approved appropriate master production and control record),

• Weights and identification codes of components,

• Dates and time of production steps,

• Identification of major pieces of equipment used in production of the batch,

• Testing results,

• Labeling,

• Initials or signatures of persons performing or checking each significant step in the operation, and

• Results of any investigations conducted.

Proposed § 212.50(d) would require production area and equipment checks to ensure cleanliness and suitability immediately before use, and a record of the checks.

Proposed § 212.50(e) specifies that process controls for PET production facilities 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.

Proposed § 212.50(f) would establish different requirements for process verification depending on whether a PET drug producer conducts full finished-product testing on a particular PET drug product:

• Proposed § 212.50(f)(1) would exempt a PET drug product from these process verification requirements if each batch of that PET drug product, prior to human administration, undergoes full finished-product testing to ensure that the product meets all specifications. For example, process verification under proposed § 212.50(f)(2) would not be required for the production of FDG F 18 where: (1) The entire batch is made in a single vial, (2) a sample from the vial is withdrawn for full finished-product testing, and (3) the finished product passes all established specifications (except for sterility) prior to human administration.

• When the results of the production of an entire batch of a PET drug product are not fully verified through finished-product testing or when only the initial sub-batch in a series is tested, process verification would be required. The PET drug producer would be required to demonstrate that the process for producing the PET drug product is reproducible and is capable of producing a drug product that meets the predetermined acceptance criteria (proposed § 212.50(f)(2)). While currently most, if not all, batches of PET drug products are fully verified through finished-product testing, future PET drug products may not be suitable for finished-product testing of an entire batch due to the short half-life of the radionuclide, and process verification would be required.

• When process verification activities are conducted, the PET drug producer would be required to document activities and results, including the date and signature of the individual(s) performing the verification, the monitoring and control methods and data, and the major equipment qualified (proposed § 212.50(f)(2)).

For a PET facility that has an established history of producing a particular PET drug product, verification of that production process may be conducted retrospectively provided that the process has not changed and has not resulted in process-related failures. However, when a PET drug product is not fully verified through finished-product testing or when only the initial sub-batch in a series is tested, process verification would be required for any new production process and after any significant change to a qualified process.

J. Laboratory Testing Requirements

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, the following requirements would apply to laboratories used to conduct testing of components, in process materials, and finished PET drug products:

• Each laboratory must have and follow written procedures for the conduct of each test and for the documentation of the results (proposed § 212.60(a)).

• Each laboratory must have sampling and testing procedures designed to ensure that components, in process materials, and PET drug products conform to appropriate standards, including established standards of identity, strength, quality, and purity (proposed § 212.60(b)).

• Laboratory analytical methods must be suitable for their intended use and must be sufficiently sensitive, specific, accurate, and reproducible (proposed § 212.60(c)).

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 recommended because many compendial methods for PET drug products lack specific information (for example, they do not describe specific equipment used), the method may not have been developed in the context of the production method actually being used, and the PET production facility may not be using the same equipment that was used in the compendial method.

• The identity, purity, and quality of reagents, solutions, and supplies used in testing must be adequately controlled, and all solutions prepared by the PET production facility must be labeled with their identity and expiration date (proposed § 212.60(d)).

• All testing equipment must be suitable for its intended purposes and capable of producing valid results (proposed § 212.60(e)).

• Each laboratory must have and follow written procedures to ensure that equipment is routinely calibrated, inspected, checked, and maintained, and these activities must be documented (proposed § 212.60(f)).

• 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 (proposed § 212.60(g)).

The records required under proposed § 212.60(g) would include the following:

- A description of the sample received for testing, including its source, the quantity, the batch or lot number, the date (and time, if appropriate) the sample was taken, and the date (and time, if appropriate) the sample was received for testing;
- A description of each method used in the testing of the sample, a record of all calculations performed in connection with each test, and a statement of the weight or measurement of the sample used for each test;
- A complete record of all data 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;
- A statement of the results of tests and how the results compare with established acceptance criteria; and
- The initials or signature of the person performing the test and the date on which the test was performed.

K. Stability

Proposed § 212.61 answers the question ''What must I do to ensure the stability of my PET drug products through expiry?'' Proposed § 212.61 would provide the following requirements to ensure the stability of PET drug products:

- PET production facilities must establish, follow, and maintain a written testing program to assess the stability characteristics of their PET drug products (proposed § 212.61(a)).
- Test methods must be reliable, meaningful, and specific (i.e., they must be capable of determining the stability characteristics of the PET drug product) (proposed § 212.61(a)).
- Samples tested for stability must be representative of the lot or batch from which they were obtained and must be stored under suitable conditions (proposed § 212.61(a)).
- Results of the stability testing must be documented and used in determining appropriate storage conditions and expiration dates and times for each PET drug product (proposed § 212.61(b)).

L. Controls and Acceptance Criteria for Finished Products

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 production facility may give final release to a finished PET drug product. We propose to establish the following requirements regarding controls and acceptance criteria:

- PET production facilities would be required to establish specifications for each batch of a PET drug product, including criteria for identity, strength, quality, purity, and, if appropriate, sterility and pyrogenicity (proposed § 212.70(a)). Most, but not all, PET drugs are sterile injectable products, and such products would be required to have specifications for sterility and pyrogenicity.
- Before a PET drug producer implements a test procedure in a specification, the producer would be required to establish and document the accuracy, sensitivity, specificity, and reproducibility of the procedure (proposed § 212.70(b)).
- If the PET drug producer uses an established compendial test procedure in a specification, the producer would be required to first verify and document that the test works under the conditions of actual use (proposed § 212.70(b)).
- PET drug producers would be required to conduct laboratory testing of a representative sample of each batch of a PET drug product before final release to ensure that the batch conforms to its specifications, except for sterility. For a PET drug product produced in 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 (proposed § 212.70(c)).
- Under proposed § 212.70(d), producers would be required to establish and follow procedures to ensure that a PET drug product is not given final release until:

—Appropriate laboratory testing under paragraph (a) of this section is completed,

—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

—A designated qualified individual 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 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. The PET production facility should document the communication of this authoritative decision to the receiving facility.

We are proposing special requirements for sterility testing because of the short half-lives of PET radionuclides. Proposed § 212.70(e) provides that:

- Sterility testing need not be completed before final release but must be performed within 30 hours after completion of production. Sterility testing should normally be started within 24 hours after production. We propose the additional 6 hours in response to the concerns of some PET drug producers that a 24-hour test initiation period would coincide with the peak activity for PET production the following day. Proposed § 212.70(e) would allow the 30-hour period to be exceeded in certain cases, such as weekends or holidays, provided it is shown that the extended period will not affect the stability or viability of the contaminants in the product or otherwise yield a potentially inaccurate result.
- 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.

We are also including in this proposal a provision to allow the conditional final release of PET drug products under certain conditions. At the September 28, 1999, public meeting on PET drug product CGMP, some comments stated that the regulations should allow PET drug producers 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 comments maintained that having duplicative equipment was difficult for smaller PET production facilities. 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.

In our preliminary draft proposed rule, we requested comments on whether the regulations should allow the conditional final release of PET drug products in case of equipment breakdown and, if so, what conditions should apply to such release. Nearly all the comments that we received on this matter requested that conditional final release be permitted. After

consideration of the comments, we propose to allow the conditional final release of PET drug products under certain conditions.

Under proposed § 212.70(f), a PET drug producer that cannot complete one of the required finished product tests for a PET drug product because of a breakdown of analytical equipment may approve the conditional final release of the product if the conditions in proposed § 212.70(f)(1) through (f)(7) are met. These conditions would require the PET drug producer to do the following:

- Have data to document that preceding consecutive batches, produced using the same method of production as the conditionally released batch, demonstrate that the conditionally released batch will likely meet the established specifications,
- Determine that all other acceptance criteria are met,
- Notify the receiving facility of the incomplete testing,
- Retain a reserve sample of the conditionally released batch of drug product,
- Complete the omitted test using the reserve sample after the analytical equipment is repaired and document that reasonable efforts have been made to ensure that the problem does not recur,
- Immediately notify the receiving facility if an out-of-specification result is obtained when testing the reserve sample, and
- Document all actions regarding the conditional final release of the drug product, including the justification for the release, all followup actions, results of completed testing, all notifications, and corrective actions to ensure that the equipment breakdown does not recur.

Conditional final release should be a rare occurrence. In general, we believe that a PET drug producer should be prepared for equipment failures. Conditional final release would not be permissible when certain types of equipment fail. If a PET drug producer could not perform a radiochemical identity/purity test on the API of a PET drug product, conditional final release of a PET drug product would not be allowed. There are, however, certain tests, such as the gas chromatography (GC)-based residual solvent determination in FDG F 18, where an equipment failure could result in the authorization of a conditional final release if all the criteria in proposed § 212.70(f) were met. Conditional final release would not generally be appropriate for certain tests where it is difficult to envision equipment failing or where equipment should be very easy to replace (for example, in the case of FDG F 18, the hydrogen-ion concentration (pH) test, test for kryptofix, thin layer chromatography based radiochemical identity and purity tests). Alternate test methods can be developed and used when these problems occur, so conditional final release should not be necessary except in very rare circumstances. Repeated conditional final releases based on the unavailability of equipment that is difficult to envision failing or that is easily replaced could be considered to be a failure to take ''reasonable efforts * * * to ensure that the problem does not recur'' and could lead to FDA taking enforcement action.

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

Proposed § 212.71 answers the question ''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 producer must identify and segregate the nonconforming product to avoid mixups.
- The producer must have and follow procedures to investigate the causes of the nonconforming product.
- The investigation must include examination of processes, operations, records, complaints, and other relevant sources of information concerning the nonconforming product.

Under the proposal, PET drug producers also would be required to:

- Document the investigation of a PET drug product that does not conform to specifications, including the results of the investigation and what happened to the rejected PET drug product (proposed § 212.71(b)), and
- Take action to correct any identified problems to prevent recurrence of a nonconforming product or other quality problem (proposed § 212.71(c)).

PET drug producers would be permitted, if appropriate, to reprocess a batch of a PET drug product that does not conform to specifications (proposed § 212.71(d)). To reprocess material that does not meet acceptance criteria:

- The producer must follow preestablished procedures (set forth in production and process controls) and
- The finished product must conform to specifications, except for sterility, before final release.

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.

N. Labeling and Packaging

Proposed § 212.80 answers the question ''What are the requirements associated with labeling and packaging PET drug products?'' Under proposed § 212.80, the following requirements would apply:

- PET drug products must be suitably labeled and packaged to protect the product from alteration, contamination, and damage during the established conditions of shipping, distribution, handling and use (proposed § 212.80(a)).
- Labels must be legible and applied so they will remain legible and affixed during the established conditions of processing, storage, handling, distribution, and use (proposed § 212.80(b)).
- Information stated on each label must also be contained in each batch production record (proposed § 212.80(c)).
- Labeling and packaging operations must be controlled to prevent product and labeling mixups (proposed § 212.80(d)).

O. Distribution Controls

Proposed § 212.90 answers the question ''What actions must I take to control the distribution of PET drug products?'' This section would primarily apply to PET production facilities that distribute PET drug products beyond the immediate vicinity of the production site. Under proposed § 212.90, PET drug producers would be required to:

- Establish, maintain, and follow written procedures for the control of distribution of PET drug products shipped from the PET production facility to ensure that shipping will not adversely affect the identity, purity, or quality of the PET drug product (proposed § 212.90(a)).
- Maintain distribution records for each PET drug product (proposed § 212.90(b)), including the following information:

—Name, address, and telephone number of the receiving facility that received each batch of a PET drug product,

—Name and quantity of the PET drug product shipped,

—Lot number, control number, or batch number for the PET drug product shipped, and

—Date and time the PET drug product was shipped.

P. Complaint Handling

Proposed § 212.100 answers the question ''What do I do if I receive a complaint about a PET drug product produced at my facility?'' We propose

the following requirements regarding complaints:

• PET drug producers must develop and follow written procedures for the receipt and handling of all complaints concerning a PET drug product (proposed § 212.100(a)).

• The procedures must include review by a designated person of any complaint involving the possible failure of a PET drug product to meet any of its specifications and an investigation to determine the cause of the failure (proposed § 212.100(b)).

• Producers must maintain a written record of each complaint in a file designated for PET drug product complaints (proposed § 212.100(c)), including the following information:

—Name and strength of the PET drug product,

—Batch number,

—Name of the complainant,

—Date the complaint was received,

—Nature of the complaint,

—Response to the complaint, and

—Findings of any investigation and followup.

• PET drug products that are returned because of a complaint may not be reprocessed and must be destroyed in accordance with applicable Federal and State law (proposed § 212.100(d)).

Q. Records

Proposed § 212.110 answers the question ''How must I maintain records of my production of PET drug products?'' Proposed § 212.110 would require that:

• PET drug producers maintain all records at the PET production facility or another location that is reasonably accessible to responsible officials of the production facility and to employees of FDA designated to perform inspections (proposed § 212.110(a)). 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.

• All records, including those not stored at the inspected establishment, be legible, stored to prevent deterioration or loss, and readily available for review and copying by FDA employees (proposed § 212.110(b)).

• PET drug producers maintain all records and documentation referenced in part 212 for at least 1 year after the final release or conditional final release of a PET drug product (proposed § 212.110(c)).

III. Analysis of Economic Impacts

We have considered the potential economic impact of this proposed rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Public Law 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize the benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity).

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing, ''any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any one year.'' The current threshold after adjustment for inflation is $115 million, using the most current (2003) Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this proposed rule to result in any 1-year expenditure that would meet or exceed this amount.

The agency has determined that this proposed rule is not an economically significant rule as described in the Executive order because annual impacts on the economy are substantially below $100 million. Under the Regulatory Flexibility Act, unless an agency certifies that a rule will not have a significant impact on a substantial number of small entities, the agency must analyze regulatory options that would minimize any significant economic impact of a rule on small entities. We project that the rule may have a significant effect on a substantial number of small entities. A regulatory flexibility analysis explaining this finding is presented in the following paragraphs.

A. Regulatory Benefits

The Modernization Act requires us to establish appropriate good manufacturing practices for PET drugs. Without minimum manufacturing standards, unintentionally inferior PET drug products may be produced for human use. The short half-life characteristic of PET drug products often limits extensive and complete finished product testing prior to administration to humans. Moreover, recalls are usually impossible due to this short half-life, which can range from minutes to hours. Most PET drug products are marketed without FDA approval, and we have not received any official reports of adverse events. Official reports that can be relied upon to demonstrate or project the actual number of adverse events related to these products therefore do not exist. Tracing infections possibly caused by contaminated PET drugs to patients is difficult since there are a multitude of other factors that can cause infections in hospitalized patients, as well as a time delay before infection presents itself. Lacking this information, we are unable to quantify this proposal's reduction of risk of adverse events associated with PET drug products and the accompanying increase in public health benefits.

This proposed rule would create minimum manufacturing standards to ensure the safety, identity, strength, quality, and purity of PET drug products. Although, as discussed in section III.B of this document, all PET drug producers have adopted some level of good manufacturing practices or SOPs, not all producers currently are fully compliant with all USP standards. Therefore, compliance with the provisions of the proposed rule would ensure that all producers establish and implement adequate SOPs for production and quality control, including internal procedures for product quality audits, resulting in consistent production of quality products. Building quality into the production process would permit early detection and correction of problems and promote continuous improvement. Activities such as developing specifications may result in increased reliability and uniformity of PET drug products to patients. Ultimately, this rule would be expected to result in a reduction in adverse reactions to PET drug products and an increase in overall benefit to the public health.

B. Regulatory Costs

All PET drug producers have already adopted some level of good manufacturing practices or SOPs, although the specificity of the written documents may vary. The Modernization Act requires that compounded PET drugs conform to USP compounding standards and official monographs for PET drugs until CGMP regulations are established for PET drugs. For producers already following required USP standards, we would expect average compliance costs associated with this proposal to be small.

The proposed CGMP rule is expected to affect all PET drug producers, especially those affiliated with hospitals and academic medical centers, as well as the small number of unaffiliated regional producers that produce FDG F 18. Most of the large corporate PET drug

producers and hospital PET drug producers associated with these corporate entities are expected to already comply to a great degree with the proposed CGMP rule. Based on our contacts with industry, we have made a general assessment of the current operational status of PET drug producers.

For this cost analysis, we consulted with the PET community, including PET drug producers and professional associations, through direct contact as well as via public comments at public meetings and previously published preliminary proposed rules (for a full description of our interactions with the PET community regarding this proposed rule, see section I.B of this document). We visited six PET drug producers affiliated with academic medical centers and four commercial (corporate or regional) operations. Using the knowledge gained from these site visits, public meeting comments from industry members including the Academy of Molecular Imaging (AMI) (a primary professional organization for PET), and agency employee expertise in PET drug manufacturing procedures, we estimated the average level of effort needed to bring each of the different types of PET drug producer into compliance with this proposed rule. Compliance costs (labor costs) were then calculated using these estimated levels of effort. In effect, we projected compliance costs based on the expected additional labor above implicit baseline levels (based on information acquired through the site visits by FDA officials).

The estimated number of U.S. establishments producing PET drug products was created by combining an AMI-prepared list of PET centers with cyclotrons with a list of PET manufacturing facilities from the Society of Nuclear Imaging in Drug Development (which has since merged with the AMI), and adding additional facilities that we identified. This resulted in the projection that the proposed rule would affect 51 producers of PET drugs, operating 101 establishments. Fifteen of these producers own or operate 65 commercial establishments (16 of which are associated with academic hospitals). Of these 15 producers, 11 are regional or local unaffiliated producers that have begun to produce PET drug products in recent years. The other four commercial producers are corporations, each of which has multiple establishments. In total, these 4 corporate producers operate 48 establishments. The remaining 36 producers are part of academic or hospital institutions (see table 1 of this document).

TABLE 1.—PET DRUG PRODUCERS

Producer Type	No. of Producers	No. of Establishments
Hospital/Academic[1]	36	36
Commercial-Regional	11	17
Commercial-Corporate[2]	4	48
Total	51	101

[1] Sixteen hospital producers operated by commercial firms are counted under Commercial-Corporate.
[2] One producer may not be a corporation but is included here due to its multiple sites and longer history of PET drug production.

C. Compliance Requirements

The proposed CGMP rule would impose compliance requirements resulting in two types of costs. From the date of publication of the final rule until the effective date, PET drug producers would incur one-time costs as each producer is brought into compliance. In succeeding years, each producer would be expected to incur only annual costs related to maintaining compliance.

The following proposed sections contain the general requirements of the rule:

- Section 212.10: Require qualified and trained personnel.
- Section 212.20: Establish SOPs to define quality assurance.
- Section 212.30: Establish SOPs and prepare documents related to installation, cleaning, qualification, and maintenance of facilities and equipment.
- Section 212.40: Establish SOPs and prepare documents on the receipt, identification, storage, handling, testing, and approval of components and drug product containers and closures. Establish specifications for the components, containers, and closures.
- Section 212.50: Establish written production and process control procedures (including in-process parameters) for production of a PET drug. Prepare master production record and batch record.
- Section 212.60: Establish written procedures and schedules for the calibration, cleaning, and maintenance of laboratory testing equipment. Establish testing procedures for components, in-process materials and finished PET drug products.
- Section 212.61: Establish written procedures to assess the stability characteristics of PET drug products.
- Section 212.70: Establish acceptance criteria and written procedures to control the release of products. Prepare SOPs to establish system suitability of each test. Prepare documents to record tests performed on the PET drug product for final release.
- Section 212.71: Establish procedures to investigate the reason for product nonconformance.
- Section 212.80: Establish templates for labeling.
- Section 212.90: Establish procedures and documents for the distribution of PET drugs.
- Section 212.100: Establish procedures for the receipt and handling of complaints regarding a PET drug product.

We expect some variation in the exact SOPs that would need to be created or revised to comply with the proposal. We expect that the various types of producers already comply with the proposed rule to different extents. The hospital PET drug producers and the independent regional commercial producers would likely require more time and effort to comply than would the group of corporate producers. Because of this, we estimated average compliance efforts for two separate groups based on expected current compliance levels—the corporate

producers and the hospital and regional commercial producers.

1. Costs to Establish SOPs

All PET drug producers are expected to incur some costs associated with interpreting the rule, determining the manner of compliance, and implementing the compliance method. These costs would be included in the efforts of a designated individual or individuals who would be primarily responsible for bringing each center into compliance. In this case, we have included any general administrative efforts in the time required to establish and write the SOPs for the previously listed requirements and to prepare templates for CGMP documentation.

The document entitled ''Sample Formats for Chemistry, Manufacturing, and Controls Sections''[1] provides guidance that may be helpful in preparing master production records, finished-product release testing records, and in-coming component tracking and testing records. PET drug producers would have the option of choosing their own format (and the amount of detail) as long as essential information required by the CGMPs is included. We believe that the CGMP guidance will aid PET drug producers that have little or no experience in creating these documents, helping to reduce compliance costs.

We estimate that all hospital and regional commercial producers will need from 3 to 5 months to establish and write detailed SOPs that comply with this rule, even with the guidance provided and the understanding that these establishments currently operate under less-detailed SOPs. We assume that the employee responsible for writing the SOPs would be in a management position, either in quality assurance or elsewhere, with a salary of up to $100,000 per year. Including an additional 35 percent for employee benefits, the cost of an average 4-month effort would amount to $45,000 for each hospital and regional commercial PET drug producer.[2]

Although most corporate PET drug producers are believed to have a complete set of SOPs, we believe each would expend some time to verify its compliance with this proposal and make minor adjustments to their SOPs. We estimate that it would take, on average, 1 month for an individual to complete the same undertaking due to the current high compliance rates expected at the corporate establishments.[3] This would result in a cost of approximately $11,250 per corporate PET drug producer, again using an estimated salary of $100,000 per year plus benefits. We assume that corporate producers with multiple manufacturing sites would amend a single set of SOPs to cover all of their production sites. Since there are currently four corporate producers of PET drug products, the cost of the SOP revisions is estimated at $45,000 (4 times $11,250).

The SOP establishment or revision work could be performed by company personnel or an outside consultant or contractor. Although we predict that the use of an outside consultant or contractor would be more likely at the hospital and regional commercial PET drug producers, we would not expect the total cost of this compliance effort to vary considerably.

Producers would also be expected to provide some additional training to at least one person on revisions made to current procedures to comply with the CGMP rule. While we do not think extensive training would be necessary at most establishments, our experience with PET drug production procedures and our 10 producer site visits leads us to believe that one person at each establishment could need up to 1 week of additional training. The cost of this additional training would amount to about $262,000 (101 establishments times 1 week at $135,000 per year).

The total cost for initial compliance associated with writing the SOPs and creating document forms amounts to approximately $2.42 million. The 47 hospital and regional commercial producers would incur a total of about $2.25 million (47 producers times $45,000 plus 53 establishments times $2,600). The 4 corporate producers would incur a total of about $170,000 (4 producers times $11,250 plus 48 establishments times $2,600). Annualizing the total one-time cost over 5 years at a 7-percent discount rate results in annualized costs of about $591,000 (at a 3-percent discount rate, the costs are estimated to be about $529,000).

Once procedures are established and documents are in place to record PET drug production and events associated with routine production of PET drugs, we would expect there to be some additional costs for the day-to-day implementation of the CGMP provisions. Periodic audits conducted by company personnel to ensure compliance with current procedures would have to be expanded to include any provisions with which the company was not already in compliance (for example, tracking and recordkeeping of incoming components, proper documentation of production and laboratory testing, tracking, investigation and documentation of products not meeting specifications). Additional time would also be spent updating the SOPs as the equipment and procedures used in the manufacture of PET drugs are upgraded and refined.

We project the day-to-day implementation of the CGMP rules would require, at most, 1 to 2 additional hours per day for an individual at each hospital or regional commercial producer. Using the midpoint of this range would result in 2.25 additional months of labor each year. Using the same estimated annual salary ($100,000 plus benefits), 2.25 months of labor equates to about $25,300 in annual costs to each PET drug production establishment, or about $1.34 million for all 53 hospital and regional commercial producer establishments. Our assessment of corporate PET drug producers is that they comply substantially with the proposed rule. For these producers, we project that 1 production individual may expend an additional 1 month of effort over the course of each year (about 3 hours per week) in order to comply with the proposed rule. This month would result in each corporate PET center incurring about $11,250 in additional annual costs, totaling $540,000 for the 48 corporate PET drug production establishments. Some producers would probably opt to use an outside consultant to manage the implementation of the new rules in the first year. Although we do not know how many producers would hire a consultant, we would not expect this to affect the total cost considerably, as the cost of the consultant would replace the cost of the company employee. Total annual costs for day-to-day implementation are estimated at $1.88 million.

Producers would also be expected to provide some additional training in future years on SOPs that were amended to comply with this CGMP rule. We would expect that this training (review for current employees as well as new employees) would be incorporated into

[1] The document is an attachment to the guidance for industry entitled ''PET Drug Applications—Content and Format for NDAs and ANDAs: Fludeoxyglucose F 18 Injection, Ammonia N 13 Injection, Sodium Fluoride F 18 Injection'' (available on the Internet at *http://www.fda.gov/cder/guidance*).

[2] Salary represents upper range of estimate (intended to not underestimate costs) provided at FDA site visit to a commercial PET drug producer on October 2, 2001. Although there is uncertainty concerning salaries paid by academic/hospital producers, we assume they would pay a salary similar to those of corporate producers.

[3] Labor hour estimate from FDA site visit to a PET drug producer on October 2, 2001.

current training programs and therefore be less burdensome to producers. Nevertheless, we have included the cost for annual training for one person per establishment for one-half week. The cost of this additional training would amount to about $131,000 (101 establishments times one-half week at $135,000 per year).

Total annual costs associated with daily implementation and training amount to $2.01 million. The 53 hospital and regional commercial establishments would incur a total of about $1.41 million (53 establishments times ($25,300 plus $1,300)). The average cost per facility for these provisions is $26,600. The 48 corporate production establishments would incur a total of about $602,000 (48 establishments times ($11,250 plus $1,300)). The average cost per facility for these provisions is $12,600.

TABLE 2.—CGMP COSTS

Rule Requirement	No. of Estab.	Labor (Months)	Wage (Yr. Sal) [1]	Cost [2]
One-Time Costs				
Establish/Write SOPs				
Academic PET Producers	47	3	$135,000	$2,115,000
Commercial PET Producers	4	1	$135,000	$45,000
Training on SOPs				
Academic PET Producers	53	0.23	$135,000	$138,000
Commercial PET Producers	48	0.23	$135,000	$125,000
Total One-Time Costs				$2,422,000
Annual Costs				
Rule Requirement				
Daily Implementation, Audits, Updates				
Academic PET Products	53	2.25	$135,000	$1,342,000
Commercial PET Products	48	1.0	$135,000	$540,000
Training				
Academic PET Products	53	0.11	$135,000	$69,000
Commercial PET Products	48	0.11	$135,000	$62,000
Total Annual Costs				$2,013,000

[1] Salary includes 35 percent increase for benefits.
[2] Cost totals may not sum to rounding.

2. Equipment Costs

Based on at least 10 site visits to PET drug production facilities (both commercial and academic) by FDA personnel, we believe that the current laboratory facilities and equipment comply with the requirements of the proposed rule. Therefore, additional costs for laboratory space or equipment would not be incurred in complying with this regulation. Further, we believe that the qualification procedures for all current production equipment already occur as a matter of current business practice, and further equipment qualification procedures would not be required.

3. Process Verification Costs

In response to public comments to the preliminary draft proposed rule, modifications have been made to the process verification requirements. For this proposed rule, all PET drug product batches that undergo full finished-product testing to ensure that the product meets specifications would not be required to verify the production process. Currently, all NDA-approved PET drug products undergo finished-product testing. We believe that all PET drug products that will receive NDA approval in the foreseeable future will undergo finished-product testing. This is because it would be difficult, using current PET drug technology, to commercialize a PET drug product with a half-life of only minutes (which would prevent finished-product testing before release). Therefore, the proposed finished-product testing requirement would not be expected to impose any additional burden in the near term. In the future, however, it is possible that some small percentage of PET drugs products with NDA approval may submit only the initial sub-batch to finished-product testing before release. In such cases, producers would have to document their process verification procedures. Since we do not know how many, if any, PET drug products such as this would be approved in the future, we are unable to estimate any additional burden to the industry from process verification requirements. Nevertheless, we believe current business practice includes process verification, so any burden to producers would result from the need to document and organize the verification activities.

4. Total Costs

Total one-time costs are estimated at about $2.42 million (annualized at $591,000 over 5 years at 7 percent, and at $529,000 at 3 percent), and annual costs at about $2.01 million (see table 3

of this document). The 53 hospital and regional commercial PET drug production establishments would incur about $2.25 million in one-time costs and $1.41 million in annual costs. The annualized (annualized one-time costs plus annual costs) cost per facility is estimated at about $35,700 at a 7-percent discount rate (and at $34,600 at 3 percent). The 48 corporate PET production facilities would incur about $170,000 and $602,000 in one-time and annual costs, respectively. Total annualized (annualized one-time costs plus annual costs) costs per corporate establishment are estimated at about $13,400 at a 7-percent discount rate (and at $13,300 at 3 percent). Total annualized costs for all producers are estimated at $2,603,000 at a 7-percent discount rate (and at $2,541,000 at 3 percent).

TABLE 3.—PET DRUG PRODUCERS' COMPLIANCE COSTS

	One-Time Cost	Annual Cost
Hospital and Regional Commercial Establishments (53)	$2,250,000	$1,410,000
Corporate Establishments (48)	$170,000	$602,000
Total Cost [1]	$2,420,000	$2,010,000
Total Annualized Cost [2]		2,600,000

[1] Sum of costs may not equal total cost due to rounding.
[2] Total annualized cost equal to total one-time cost discounted at 7-percent over 5 years plus total annual cost. Using a 3-percent discount rate reduces annualized costs by about $60,000.

D. Growth of the PET Industry

Although we do not have reliable estimates of the annual number of PET scans, the number has increased dramatically over the last 10 years, due at least in part to the increased numbers of disease conditions for which both public and private insurers have extended coverage. The number of establishments producing PET drug products, and FDG F 18 in particular, has also increased over this time period. As mentioned previously in this document, the majority of this growth in establishments reflects commercial operations that focus mainly or solely on FDG F 18 production.

As demand for PET scan services and, therefore, PET drug products is expected to continue to increase, we have projected compliance costs over the next 10 years. We cannot confidently predict the number of additional PET drug production runs to meet the additional demand for PET services because of unknown factors. We do not know the number of additional diseases for which PET will be used and be reimbursable in the future or possible increases in size of production batches of PET drugs. Because PET drug producers are not currently producing to capacity, we believe that increased demand would be partially met by increasing production runs and batch sizes at existing establishments rather than proportional increases in the number of PET production establishments. We have therefore tentatively projected that average annual PET drug production establishment increases would range from 3 to 7 percent. Assuming this growth occurs evenly across producer types, this growth rate implies an increase in annualized costs from $2.60 million currently to $3.40 to $4.79 million in year ten (with a present value of $3.37 million at a 7-percent discount rate, and $3.64 million at a 3-percent discount rate). The PET drug risk reduction resulting from this rule would also apply to the additional volume of PET drug dosages implied by the 3 to 7 percent annual growth rate in PET drug establishments. We request public comment and data on the annual number of PET scans and the expected future growth rate of PET drug products and production establishments subject to this proposed rule.

E. Regulatory Flexibility Analysis

The Regulatory Flexibility Act requires agencies to examine regulatory alternatives for small entities if that rule may have a significant impact on a substantial number of small entities.

1. Objective of the Rule

The implementation of this proposed rule, in accordance with the Modernization Act, would help ensure the safety, identity, strength, quality, and purity of PET drugs by establishing CGMP. The objective of the proposal is to reduce the risk to public health from adverse events that would be more likely to occur in the absence of adherence to CGMP for PET drug products.

2. Definition of Small Entities

A regulatory flexibility analysis (RFA) is required to estimate the number of small entities to which the proposed rule would apply. Under the Regulatory Flexibility Act (as amended), the definition of a small entity would include a small business as defined under the Small Business Administration (SBA) Act, nonprofit organizations, and small governmental jurisdictions.

This rule would affect producers of PET drug products. These include certain hospitals, clinics, colleges and universities, and producers of in vivo diagnostic substances. According to the SBA, pharmaceutical preparation manufacturers with 750 or fewer employees, electromedical and electrotherapeutic apparatus manufacturers with 500 or fewer employees, drugs and druggists' sundries wholesalers with 100 or fewer employees, and for-profit hospitals, clinics, colleges, and universities with $29 million or less in revenue are considered small businesses or entities. As stated earlier in this analysis, we identified 101 establishments operated by 51 PET drug producers. In over one-third of the cases, the PET drug product is produced by a hospital. In other instances, a corporate producer manages production under contract at one or more hospitals with cyclotrons. PET drug products are also produced at independent establishments by corporate producers or small regional producers. Total producer numbers continue to increase as the current corporate producers expand their

number of establishments and more independent regional producers enter the market.

Using information from the American Hospital Association (AHA), we characterized 28 of the hospital producers as one of the following establishment types:

- Government, non-Federal;
- Government, Federal;
- Non-Government not-for-profit; and
- Investor-owned (for-profit).[4]

The AHA data did not include information for eight hospitals associated with large colleges or universities, but for this analysis, these were assumed to be not-for-profit because approximately 93 percent of all 4-year higher education institutions are public or nonprofit institutions.[5] Census data reports indicate that private hospitals (with more than 100 employees) average gross revenues of about $36.8 million in 1997. This figure inflates to about $46.0 million using the Consumer Price Index (CPI) for medical care from 1997 to 2003. Considering that hospitals producing PET drug products would probably be larger than the average private hospital, we consider it very likely that the two private hospitals producing PET drugs have annual revenues over $29 million and would therefore not be considered small entities.[6] In instances where PET drug producer information is not available, this analysis assumes that the PET drug producer is owned by the hospital in which it is located.

Two of the three domestic corporate PET drug producers exceed the SBA employee limits within their respective business classifications to qualify as small businesses. Employee data were not available for the other domestic corporation or any of the 11 regional commercial producers, and we therefore assume that these may be small businesses.

In total, the 51 identified producers of PET drug products are classified as follows: 6 Federal, 6 State, 34 small entities, and 5 large entities. Most of those that were considered small entities were classified as such because they are not-for-profit organizations, not because they met the employee or revenue limits for small businesses. It should be noted that an entity's identification as small or large in this analysis does not necessarily indicate the volume of PET drug products it produces or the share of the market it holds.

3. Impact on Small Entities

Another requirement of an RFA is that we estimate the reporting, recordkeeping, and other compliance requirements on small entities. These requirements are detailed in the regulatory cost section of this preamble. Most, if not all, of the PET drug producers currently employ individuals who possess skills necessary to establish written procedures and prepare documentation as required by this rule. Some may choose, as mentioned above, to contract with an outside consultant to manage their compliance with the rule.

At most, a single-establishment PET drug producer may incur one-time and annual costs of approximately $42,500 and $25,300 per operating facility, respectively. The hospital and regional commercial producers would incur these higher per-facility costs because these establishments are expected to require more time to fully comply with the written procedure and recordkeeping requirements. The total of the maximum one-time and annual costs per producer equates to significantly less than 1 percent of the $88 million ($70.8 million inflated by the CPI for medical care from 1997 until 2003) average annual gross revenue per nonprofit hospital. In addition, most of the hospitals that would be affected by this rule are affiliated with large universities whose total revenues are expected to be much higher than the $88 million figure cited. The estimated compliance cost would represent an even smaller portion of a percent of the entire university's revenues. Revenue data were not available for the one possibly small corporate producer. This company would incur annual costs of approximately $62,700 and one-time costs of about $24,000. The 11 regional commercial producers are expected to incur one-time and annual costs of approximately $42,500 per producer and $25,300 per operating facility, respectively. We lack sufficient data to estimate the expected compliance costs as a percent of revenues for the regional commercial producers. Accordingly, it is possible that this proposed rule might have a significant effect on these small entities. We request comment on the extent of the effect that this rule will have on small entities, as well as additional data to profile PET drug producers.

4. Other Federal Rules

We are not aware of any relevant Federal rules that may duplicate, overlap, or conflict with the proposed rule. We request any information that may show otherwise.

5. Description of Alternatives

Several alternative provisions were considered but not adopted during the formulation of this rule.

Traditional CGMP. We considered requiring PET drug producers to follow traditional CGMP (parts 210 and 211), but because these requirements would not allow the flexibility of PET drug CGMP detailed in this rule, the compliance costs would have been much greater under this alternative. The increased flexibility provided by this proposal is believed to be more appropriate because of the special characteristics of PET drugs, including their short half-life, small-scale manufacturing, and limited distribution environment.

Specific identity testing of PET drug components. We were also interested in preventing contamination of PET drugs with components that may present a threat to public health. We therefore considered an alternative that would have required specific identity testing of PET drug components. In the May 2002 preliminary proposed rule, we proposed that PET drug producers perform identity testing on raw materials that yield a drug substance and each inactive ingredient that is not a finished drug product. For FDG F 18 production, this would have required that mannose triflate be tested using either infrared spectroscopy (IR) or nuclear magnetic spectroscopy (NMR). We were unable to estimate the current level of compliance with this provision and therefore assumed the level to be zero, although it is possible that some PET drug producers currently perform this testing. Contact with PET drug producers indicated that the most probable method of compliance would have been to use a private laboratory to perform these tests under contract to the PET drug producers. Although some producers, especially hospital producers, may have IR testing equipment or could at least acquire these services from other departments at their institutions, we assumed they would also use the services of private laboratories.

We estimated that producers receive from two to six lots of mannose triflate annually, and we believe the average number is around three. We have estimated the costs of the identity testing alternative assuming the use of NMR. Since testing could be done using

[4] ''AHA Guide to the Health Care Field, 1997–98 Edition.'' Healthcare Infosource, Inc., a subsidiary of the American Hospital Association.

[5] ''The Nation: Colleges and Universities,'' *The Chronicle of Higher Education, 1999–2000, Almanac Issue*, volume XVI, no. 1, p. 7, August 27, 1999.)

[6] ''Hospital Statistics,'' table 3, pp. 8–9, Health Forum, An American Hospital Association Company, 1999.

either IR or NMR, with IR being somewhat less expensive, our estimates may overstate actual costs. Sample testing using the NMR is expected to cost up to $400 including the additional consultation and interpretation of the results with the technical staff. Testing three lots per year would result in a cost of $1,200 to each PET drug producer. We estimate that the total annual cost of identity testing the mannose triflate would have been about $121,000 for all PET drug producers.

Identity testing of O 18 water would be performed through the cyclotron production run and is believed to be current practice. Therefore, no additional compliance costs would have been added for identity testing of the O 18 water.

Many of the hospital PET producers make a small number of additional PET drug products and may use other inactive ingredients. Almost all excipients and other components are marketed as finished drug products and would not have required identification testing under this alternative policy. We do not have enough data to estimate confidently the average number of additional PET drug products made by each establishment, but we conservatively project that two components would require identity testing at each of the 36 hospital PET producers as well as the 16 hospital producers operated by corporate producers. Identity testing of these additional components would have added an additional $2,400 per PET drug producer (2 components times $400 per test times 3 lots per year), resulting in a total of about $125,000 in costs to the industry ($2,400 times 36 academic and hospital producers plus 16 hospital producers operated by industry). The total cost of identity testing of components would have amounted to about $246,000 ($121,000 for mannose triflate and $125,000 for the other components). The regional commercial PET drug producers and the corporate producers (excluding hospital producers operated by corporate entities) are believed to produce only FDG F 18. These producers would have incurred no additional costs under this alternative.

PET drug producers commented that this alternative requirement would still be unnecessary and unduly burdensome because components and contaminants would be identified in finished-product testing and a certificate of analysis is provided by the supplier. We are in substantial agreement with these comments and have removed the component identity testing requirement from the proposed rule.

Verification of the certificate of analysis. A related alternative, also proposed in the preliminary draft proposed rule of May 2002, would have required producers to verify the component specifications as written on the certificate of analysis. We believe that certificate of analysis verification would also be completed by independently testing the first three lots of each component received. We estimate that this would require contract testing of about three components for the hospital and regional commercial producers and about two components for the corporate producers. The total cost associated with verifying the reliability of the component suppliers would be a one-time cost of about $306,000. This would include $3,600 (3 lots times 3 components times $400) for each hospital and regional commercial producer establishment for a total of $191,000, and about $2,400 (3 lots times 2 components times $400) for corporate producer establishments for a total of about $115,000. Using a discount rate of 7 percent over 5 years, the annualized cost would have amounted to about $75,000.

Several PET drug producers commented that a requirement for verification of the supplier's certificate of analysis would also be unnecessary and unduly burdensome. They stated that an established track record with a supplier showing no problems in finished-product test results should adequately establish the reliability of a supplier. As with the component identity testing alternative, we are in substantial agreement with PET drug producer comments and have not included the certificate of analysis verification requirement in the proposed rule.

Validation of production and process controls. We also considered a requirement that production and process controls in every PET drug production process be validated according to established procedures. This provision was included in the preliminary draft proposed rule. It would have provided for retrospective validation in most cases, which would have relied on a review of historical data to show that each process is sufficiently capable of yielding batches meeting specifications. PET drug producers commented that this provision would be unnecessarily burdensome for those producers without written validation protocols, and finished-product testing would alleviate the safety concerns. After considering these comments, we decided not to include this provision in the proposed rule. While we did not calculate a separate cost for this provision, we believe it could have been burdensome for some producers.

Audit trail capabilities. Another alternative would have been to require audit trail capabilities for all computer-operated systems to ensure the security of all production and nonproduction records. For nonproduction systems, software is available with audit trail capabilities and can be run alongside a widely used spreadsheet software program. This additional software system would provide PET producers with audit trail capabilities for tracking the receipt of drug components and in-process materials, the distribution of finished products, batch records, complaint files, personnel training, and equipment maintenance. Prices for this software, including its base price, a validation package, and annual maintenance and support, are available on the Internet. The entire package would amount to about $7,000 in first year costs for a PET drug producer. A short training course provided by the software vendor would increase first year costs by about $1,600 for each producer. In order to account for some uncertainty and regional price differences for this or similar software programs, we increased the estimated costs about 50 percent. Compliance costs would therefore be expected to total about $12,900 for each PET drug producer ($10,400 for the base license, validation package, and first year maintenance and support plus about $2,400 for a short training program). We believe there is very little use of software providing secure audit trail capabilities. Therefore, we assumed that to comply with this provision, all PET drug producers would have had to purchase software providing secure audit trail capabilities. The total first year cost of this software would have been about $1,303,000 for the 101 PET drug production establishments. We further assumed that 50 percent of the producers would need to purchase the spreadsheet software at a cost of about $150 each, adding $7,600 to the software costs. Total one-time software costs for non-production equipment would have been about $1,310,000.

The manufacturers of the audit-trail capable software would also have been expected to provide on-site maintenance and support of their systems, as mentioned above. PET drug producers would have been expected to purchase these maintenance and support systems. Based on our contact with one such software manufacturer, we estimated that the annual cost of such a system would be about $1,000 per year. In order to account for the uncertainty in using

only a single software application in estimating costs, we increased this amount to about $1,500 for each PET drug producer for this analysis. The estimated total cost for all 101 producers would have been about $152,000 annually.

We also considered requiring the radiochemical synthesis apparatus, as well as the HPLC and GC equipment, to have secure audit trail software systems with electronic signature capabilities. We believe that most of this equipment and programming software currently provides date, time, and employee identification capabilities. However, for at least some producers we believe that a software update would be required to provide, at a minimum, file deletion prevention capabilities. While software packages are updated regularly in the industry, we did not have enough information to estimate the incremental cost of updating all types of production equipment software to include audit trail capabilities. Information on electronic recordkeeping, which would apply to electronic audit trails, may be found in 21 CFR part 11; Electronic Records; Electronic Signatures and the draft guidance document entitled ''PET Drug Products—Current Good Manufacturing Practice (CGMP).'' We invite public comment and data on the scope and cost of creating electronic audit trail capability, including data on current audit trail capabilities within the industry.

The electronic audit trail requirements we have described were excluded from the proposed rule because we could not determine if the additional level of quality assurance would justify the additional compliance costs. We request public comment and data concerning the need for electronic audit trail requirements as part of the CGMPs for PET drug products.

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

This proposed rule contains information collection requirements that are subject to review by OMB under the Paperwork Reduction Act of 1995 (the PRA) (44 U.S.C. 3501–3520). The title, description, and respondent description of the information collection provisions are shown below with an estimate of the annual reporting and recordkeeping burden. Included in the estimate is the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each collection of information.

We invite comments on these topics: (1) Whether the collection of information is necessary for the proper performance of our functions, including whether the information will have practical utility; (2) the accuracy of our estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

Title: Current Good Manufacturing Practice for Positron Emission Tomography Drugs

Description: In accordance with the Modernization Act, the proposed rule would establish CGMP requirements for PET drugs. The proposed CGMP requirements are designed to take into account the unique characteristics of PET drugs, including their short half-lives and the fact that most PET drugs are produced at locations that are very close to the patients to whom the drugs are administered. The estimate is based on there being 51 PET drug producers operating 36 hospital or academic facilities and 65 commercial facilities for a total of 101 PET drug production facilities.

The proposed regulations are intended to ensure that approved PET drug products meet the requirements of the act as to safety, identity, strength, quality, and purity. The proposed regulations address the following matters: Personnel and resources; quality control; facilities and equipment; control of components, in-process materials, and finished products; production and process controls; laboratory controls; acceptance criteria; labeling and packaging controls; distribution controls; complaint handling; and recordkeeping.

The proposed CGMP regulations would establish several recordkeeping requirements for the production of PET drugs. In making our estimates of the time spent in complying with these proposed requirements, we relied on communications we have had with PET producers, visits by our staff to PET facilities, and our familiarity with both PET and general pharmaceutical manufacturing practices.

Description of Respondents: Academic institutions, hospitals, commercial manufacturers, and other entities that produce PET drug products.

Burden Estimate: Table 4 of this document provides an estimate of the annual recordkeeping burdens associated with the proposed rule. We are not proposing any reporting requirements. All of our recordkeeping burden estimates are based on there being 101 PET production facilities, with each of the 36 academic or hospital facilities producing 3 different PET drug products and each of the 65 commercial facilities producing 1 PET drug product, resulting in an estimated 173 total PET drug products. Our estimates are also based on a 250-day work year with an average yearly production of 500 batches for each facility. We have also taken into account that time spent on recording procedures, processes, and specifications may be somewhat higher in the year in which these records are first established and correspondingly lower in subsequent years, when only updates and revisions would be required.

A. Investigational and Research PET Drug Products

Proposed § 212.5(b)(2) provides that for investigational PET drugs or drug products produced under an IND and research PET drugs or drug products produced with approval of an RDRC, the requirement under the act to follow current good manufacturing practice is met by complying with USP 28 Chapter <823>. We believe that PET production facilities producing drugs under INDs and RDRCs are currently substantially complying with the recordkeeping requirements of USP 28 Chapter <823> (see section 121(b) of the Modernization Act), and accordingly, we have not estimated any recordkeeping burden for this provision of this proposed rule.

B. Batch Production and Control Records

Proposed §§ 212.20(c) through (e), 212.50(a) through (c), and 212.80(c) set out requirements for batch and production records as well as written control records. We estimate that it would take 20 hours annually for each PET production facility to prepare and maintain written production and control procedures and to create and maintain master batch records for each PET drug product produced. We also estimate that there will be a total of 173 PET drug products produced, with a total estimated recordkeeping burden of 3,460 hours. We estimate that it would

take a PET production facility an average of 30 minutes to complete a batch record for each of 500 batches. Our estimated burden for completing batch records is 25,250 hours.

C. Equipment and Facilities Records

Proposed §§ 212.20(c), 212.30(b), 212.50(d), and 212.60(f) contain requirements for records dealing with equipment and physical facilities. We estimate that it would take 1 hour to establish and maintain these records for each piece of equipment in each PET production facility. We estimate that the total burden for establishing procedures for these records would be 1,515 hours. We estimate that recording maintenance and cleaning information would take 5 minutes a day for each piece of equipment, with a total recordkeeping burden of 31,436 hours.

D. Records of Components, Containers, and Closures

Proposed §§ 212.20(c), 212.40(a) through (b) and (e) contain requirements on records regarding receiving and testing of components, containers, and closures. We estimate that the annual burden for establishing these records would be 202 hours. We estimate that each facility would receive 36 shipments annually and would spend 10 minutes per shipment entering records. The annual burden for maintaining these records would be 604 hours.

E. Process Verification

Proposed § 212.50(f)(2) would require that any process verification activities and results be recorded. Because process verification would only be required when results of the production of an entire batch are not fully verified through finished-product testing, we believe that process verification will be a very rare occurrence, and we have not estimated any recordkeeping burden for documenting process verification.

F. Laboratory Testing Records

Proposed §§ 212.20(c), 212.60(a) through (b) and (g), 212.61(a) through (b), and 212.70(a) through (b) and (d) set out requirements for documenting laboratory testing and specifications referred to in laboratory testing, including final release testing and stability testing. We estimate that each commercial PET production facility will need to establish procedures and create forms for 20 different tests for the 1 product they produce. Each hospital and academic PET drug production facility will need to establish procedures and create forms for a total of 34 different tests for the 3 products they produce. We estimate that it will take each facility an average of 1 hour to establish procedures and create forms for one test. The estimated annual burden for establishing procedures and creating forms for these records would be 2,525 hours, and the annual burden for recording laboratory test results would be 8,383 hours.

G. Sterility Test Failure Notices

Proposed § 212.70(e) would require PET drug producers to notify all receiving facilities if a batch fails sterility tests. We also believe that sterility test failures will be a very rare occurrence, and we have estimated no recordkeeping burden for the notices. If such an event were to occur, we believe that PET drug producers would use e-mail and facsimile transmission to notify the receiving facilities of the test failure. Providing notice should take less than 1 hour per failure.

H. Conditional Final Releases

Proposed § 212.70(f) would require PET drug producers to document any conditional final releases of a product. We believe that conditional final releases would be fairly uncommon, but for purposes of the PRA, we have estimated that each PET production facility would have one conditional final release a year and would spend 1 hour documenting the release and notifying receiving facilities.

I. Out-of-Specification Investigations

Proposed §§ 212.20(c) and 212.71(a) and (b) would require PET drug producers to establish procedures for investigating products that do not conform to specifications and conduct these investigations as needed. We estimate that it would take 1 hour annually to record and update these procedures for each PET production facility. We also estimate, for purposes of the PRA, that one out-of-specification investigation would be conducted at each facility each year and that it would take 1 hour to document the investigation.

J. Reprocessing Procedures

Proposed §§ 212.20(c) and 212.71(d) would require PET drug producers to establish and document procedures for reprocessing PET drug products. We estimate that it would take 1 hour a year to document these procedures for each PET production facility. We have not estimated a separate burden for recording the actual reprocessing, both because we believe it would be an uncommon event and because the recordkeeping burden has been included in our estimate for batch production and control records.

K. Distribution Records

Proposed §§ 212.20(c) and 212.90(a) would require that written procedures regarding distribution of PET drug products be established and maintained. We estimate that it would take 1 hour annually to establish and maintain records of these procedures for each PET production facility. Proposed § 212.90(b) would require that distribution records be maintained. We estimate that it would take 15 minutes to create an actual distribution record for each batch of PET drug products, with a total burden of 1,375 hours for all PET producers.

L. Complaints

Proposed §§ 212.20(c) and 212.100 would require that PET drug producers establish written procedures for dealing with complaints, as well as document how each complaint is handled. We estimate that establishing and maintaining written procedures for complaints would take 1 hour annually for each PET production facility and that each facility would receive one complaint a year and would spend 30 minutes recording how the complaint was dealt with.

We invite comments on this analysis of information collection burdens.

TABLE 4.—ESTIMATED ANNUAL RECORDKEEPING BURDEN [1]

21 CFR Section	No. of Recordkeepers	Annual Frequency per Recordkeeping	Total Annual Records	Hours per Recordkeeper	Total Hours
212.20(c) and (e), 212.50(a) and (b)	101	1.71	173	20	3,460

TABLE 4.—ESTIMATED ANNUAL RECORDKEEPING BURDEN [1]—Continued

21 CFR Section	No. of Recordkeepers	Annual Frequency per Recordkeeping	Total Annual Records	Hours per Recordkeeper	Total Hours
212.20(d) and (e), 212.50(c), 212.80(c)	101	500	50,500	.5	25,250
212.20(c), 212.30(b), 212.50(d), 212.60(f)	101	15	1,515	1	1,515
212.30(b), 212.50(d), 212.60(f)	101	3,750	378,750	.083	31,436
212.20(c), 212.40(a) and (b)	101	2	202	1	202
212.40(e)	101	36	3,636	.166	604
212.20(c), 212.60(a) and (b), 212.61(a), 212.70(a), (b), and (d)	101	25	2,525	1	2,525
212.60(g), 212.61(b), 212.70(d)(2) and (d)(3)	101	500	50,500	.166	8,383
212.70(f)	101	1	101	1	101
212.20(c), 212.71(a)	101	1	101	1	101
212.71(b)	101	1	101	1	101
212.20(c), 212.71(d)	101	1	101	1	101
212.20(c), 212.90(a)	101	1	101	1	101
212.90(b)	101	500	50,500	.25	12,625
212.20(c), 212.100(a)	101	1	101	1	101
212.100(b) and (c)	101	1	101	.5	50
Total					86,656

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.

In compliance with the PRA, we have submitted the information collection requirements of this proposed rule to OMB for review. Interested persons are requested to send comments regarding information collection to the Office of Information and Regulatory Affairs, OMB.

Submit written comments on the information collection provisions to the Office of Information and Regulatory Affairs, OMB. OMB is still experiencing significant delays in the regular mail, including first class and express mail, and messenger deliveries are not being accepted. To ensure that comments on the information collection are received, OMB recommends that written comments be faxed to the Office of Information and Regulatory Affairs, OMB, Attn: Fumie Yokota, Desk Officer for FDA, FAX: 202–395–6974.

VI. Federalism

We have analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. We have tentatively determined that the rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Consequently, we do not currently plan to prepare a federalism summary impact statement for this rulemaking procedure. We invite comments on the federalism implications of this proposed rule.

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

VIII. Comments

Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) written or electronic comments regarding this proposal. Submit a single copy of electronic comments or two paper copies of any mailed comments, except that individuals may submit one paper 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 Division

of Dockets Management 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 practice, Drugs, Incorporation by reference, Labeling, Laboratories, Packaging and containers, Positron emission tomography drugs, Prescription drugs, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act, the Food and Drug Modernization Act of 1997, and under authority delegated to the 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; 42 U.S.C. 216, 262, 263a, 264.

§ 210.1 [Amended]

2. Amend § 210.1(a), (b), and (c) by removing the phrase ''211 through 226'' each time it appears and by adding in its place the phrase ''211, 225, and 226''.

§ 210.2 [Amended]

3. Amend § 210.2(a) and (b) 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 in paragraphs (a) and (b) introductory text by removing the phrase ''211 through 226'' and adding in its place the phrase ''211, 225, and 226''.

PART 211—CURRENT GOOD MANUFACTURING PRACTICE FOR FINISHED PHARMACEUTICALS

5. 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; 42 U.S.C. 216, 262, 263a, 264.

6. 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 PRACTICE FOR POSITRON EMISSION TOMOGRAPHY DRUGS

Subpart A—General Provisions

Sec.

Subpart B—Personnel and Resources

Subpart C—Quality Assurance

Subpart D—Facilities and Equipment

Subpart E—Control of Components, Containers, and Closures

Subpart F—Production and Process Controls

Subpart G—Laboratory Controls

Subpart H—Finished Drug Product Controls and Acceptance Criteria

Subpart I—Packaging and Labeling

Subpart J—Distribution

Subpart K—Complaint Handling

Subpart L—Records

Authority: 21 U.S.C. 321, 351, 352, 355, 371, 374; Sec. 121, Pub. L. 105–115, 111 Stat. 2296.

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 or monitoring of a disease or a manifestation of a disease in humans, but does not include 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.

Batch production and control record means a unique record that references an accepted master production and control record and documents specific details on production, labeling, and quality control for a single batch of a PET drug product.

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.

Conditional final release means a final release made prior to completion of a required finished product test because of a breakdown of analytical equipment.

Final release means the authoritative decision by a responsible person in a PET production facility to permit the use of a batch of a PET drug product in humans.

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

In-process material means any material fabricated, compounded, blended, or derived by chemical reaction that is produced for, and is used in, the preparation of a PET drug product.

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 from which the complete history of the production, processing, packing, holding, and distribution of a batch or lot 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 by a responsible person in a PET production facility 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 drug means a radioactive 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. The definition includes any nonradioactive reagent, reagent kit, ingredient, nuclide generator, accelerator, target material, electronic synthesizer, or other apparatus or computer program to be used in the preparation of a PET drug.

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

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

*Production*means the manufacturing, compounding, processing, 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.

Receiving facility means any hospital, institution, nuclear pharmacy, imaging facility, or other entity or part of an entity that accepts a PET drug product that has been given final release, but does not include a common or contract carrier that transports a PET drug product from a PET production facility to a receiving facility.

Specifications means the tests, analytical procedures, and appropriate acceptance 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, meets the listed acceptance criteria.

Strength means the concentration of the active pharmaceutical ingredient (radioactivity amount per volume or weight at the time of calibration).

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

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

Current good manufacturing practice for PET drug products is the minimum requirements for the methods to be used in, and the facilities and controls used for, the production, quality control, holding, or distribution of PET drug products intended for human use. Current good manufacturing practice is intended 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.

§ 212.5 To what drugs do the regulations in this part apply?

(a) *Application solely to PET drug products.* The regulations in this part apply only to the production, quality control, holding, and distribution 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 current good manufacturing practice requirements in parts 210 and 211 of this chapter. The regulations in this part apply to all PET drug products for human use except for investigational and research PET drugs as described in paragraph (b) of this section.

(b) *Investigational and research PET drugs.* The regulations in this part do not apply to investigational PET drugs or drug products for human use produced under an investigational new drug application in accordance with part 312 of this chapter and PET drugs or drug products produced with the approval of a Radioactive Drug Research Committee in accordance with part 361 of this chapter. For such investigational and research PET drugs or drug products, the requirement under the act to follow current good manufacturing practice is met by producing PET drugs or drug products in accordance with Chapter 823, ''Radiopharmaceuticals for Positron Emission Tomography—Compounding,'' of the 28th edition of the United States Pharmacopeia (2005), which is incorporated by reference. The Director of the Office of the Federal Register approves this incorporation by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51. You may obtain copies from the United States Pharmacopeial Convention, Inc., 12601 Twinbrook Pkwy., Rockville, MD 20852, or you may examine a copy at the Center for Drug Evaluation and Research's Division of Medical Library, 5600 Fishers Lane, rm. 11B–40, Rockville, MD, or at the National Archives and Records Administration (NARA). For information on the availability of this material at NARA, call 202–741–6030, or go to: *http://www.archives.gov/federal__register/code__of__federal__regulations/ibr__locations.html*.

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

Subpart C—Quality Assurance

§ 212.20 What activities must I perform to ensure product quality?

(a) *Production operations.* You must 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) *Materials.* You 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) *Specifications and processes.* You must approve or reject, before implementation, any initial specifications, methods, processes, or procedures, and any proposed changes to existing specifications, methods, processes, or procedures, to ensure that they maintain the identity, strength, quality, and purity of a PET drug. You must demonstrate that any change does not adversely affect the identity, strength, quality, or purity of any PET drug product.

(d) *Production records.* You must review production records to determine whether errors have occurred. If errors have occurred, or a production batch or any component of the batch fails to meet any of its specifications, you must determine the need for an investigation, conduct investigations when necessary, and take appropriate corrective actions.

(e) *Quality assurance.* You must establish and follow written quality assurance procedures.

Subpart D—Facilities and Equipment

§ 212.30 What requirements must my facilities and equipment meet?

(a) *Facilities.* You must provide adequate facilities to ensure the orderly handling of materials and equipment, the prevention of mixups, 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) *Equipment procedures.* 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, properly installed, maintained, and capable of repeatedly producing valid results. You must document your activities in accordance with these procedures.

(c) *Equipment construction and maintenance.* 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, login, 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 tested or examined to determine whether the lot complies with your specifications. You must not use in PET drug product 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. You must use a reliable supplier as a source of each lot of each component, container, and closure.

(1)(i) If you conduct finished-product testing of a PET drug product that includes testing to ensure that the correct components have been used, you must determine that each lot of incoming components used in that PET drug product complies with written specifications by examining a certificate of analysis provided by the supplier. You are not required to perform a specific identity test on any of those components.

(ii) If you do not conduct finished-product testing of a PET drug product that ensures that the correct components have been used, you must conduct identity testing on each lot of a component that yields an active ingredient and each lot of an inactive ingredient used in that PET drug product. This testing must be conducted using tests that are specific to each component that yields an active ingredient and each inactive ingredient. For any other component, such as a solvent or reagent, that is not the subject of finished-product testing, you must determine that each lot complies with written specifications by examining a certificate of analysis provided by the supplier; if you use such a component to 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. However, if you use as an inactive ingredient a product that is approved under section 505 of the act (21 U.S.C. 355) and is marketed as a finished drug product intended for intravenous administration, you need not perform a specific identity test on that ingredient.

(2) 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, mixups, 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 (where applicable).

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

(b) *Master production and control records.* You must have master production and control records that document all steps in the PET drug product production process. The master production and control records must include the following information:

(1) The name and strength of the PET drug product;

(2) If applicable, the name and radioactivity or other measurement of each active pharmaceutical ingredient and each inactive ingredient per batch or per unit of radioactivity or other measurement of the drug product, and a statement of the total radioactivity or other 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 specified in the master production and control records;

(6) A statement of acceptance criteria on radiochemical yield, i.e., the minimum percentage 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.

(c) *Batch production and control records.* 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) Name and strength of the PET drug product;

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

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

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

(5) Weights (or other measure of quantity) and identification codes of components;

(6) Dates and time of production steps;

(7) Identification of major pieces of equipment used in production of the batch;

(8) Testing results;

(9) Labeling;

(10) Initials or signatures of persons performing or checking each significant step in the operation; and

(11) Results of any investigations conducted.

(d) *Area and equipment checks.* The production area and all equipment in the production area 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) *Process verification.* (1) For a PET drug product for which each entire batch undergoes full finished-product testing to ensure that the product meets all specifications, process verification, as described in paragraph (f)(2) of this section, is not required.

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

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

(b) *Specifications and standards.* Each laboratory must have sampling and testing procedures designed to ensure that components, 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 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 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, if appropriate) the sample was taken, and the date (and time, if appropriate) 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 the date and time the test was conducted, 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?

(a) *Stability testing program.* 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 for stability must be representative of the lot or batch from which they were obtained and must be stored under suitable conditions.

(b) *Storage conditions and expiration dates.* 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 new test procedure in a specification, you must establish and document the accuracy, sensitivity, specificity, and reproducibility of the procedure. If you use an established compendial test procedure in a specification, you must first verify and document that the test works under the conditions of actual use.

(c) *Conformance to specifications.* Before final release, you must conduct laboratory testing of a representative sample of each batch of a PET drug product to ensure that the product conforms to specifications, except for sterility. 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 the following is done:

(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 30 hours after completion of production. The 30-hour requirement may be exceeded due to a weekend or holiday. If the sample for sterility testing is held longer than indicated, you must demonstrate that the longer period does not adversely affect the sample and the test results obtained will be equivalent to test results that would have been obtained if the test had been started within the 30-hour time period. 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. The notification must be documented.

(f) *Conditional final release.* (1) If you cannot complete one of the required finished product tests for a PET drug product because of a breakdown of analytical equipment, you may approve the conditional final release of the product if you meet the following conditions:

(i) You have data documenting that preceding consecutive batches, produced using the same methods used for the conditionally released batch, demonstrate that the conditionally released batch will likely meet the established specifications;

(ii) You determine that all other acceptance criteria are met;

(iii) You immediately notify the receiving facility of the incomplete testing;

(iv) You retain a reserve sample of the conditionally released batch of drug product;

(v) You complete the omitted test using the reserve sample after the analytical equipment is repaired and you document that reasonable efforts have been made to ensure that the problem does not recur;

(vi) If you obtain an out-of-specification result when testing the reserve sample, you immediately notify the receiving facility; and

(vii) You document all actions regarding the conditional final release of the drug product, including the justification for the release, all followup actions, results of completed testing, all notifications, and corrective actions to ensure that the equipment breakdown does not recur.

(2) Even if the criteria in paragraph (f)(1) of this section are met, you may not approve the conditional final release of the product if the breakdown in analytical equipment prevents the performance of a radiochemical identity/purity test.

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

(a) *Rejection of a nonconforming product.* You must reject a batch of a PET drug product that does not conform to specifications. You must have and follow procedures to identify and segregate the product to avoid mixups. 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) *Investigation.* 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) *Correction of problems.* You must take action to correct any identified problems to prevent recurrence of a nonconforming product or other quality problem.

(d) *Reprocessing.* 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, except for sterility, before final release.

Subpart I—Packaging and Labeling

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

(a) A PET drug product must be suitably labeled and packaged to protect the product from alteration, contamination, and damage during the established conditions of shipping, distribution, handling, and use.

(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 also be contained in each batch production record.

(d) Labeling and packaging operations must be controlled to prevent labeling and product mixups.

Subpart J—Distribution

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

(a) *Written distribution procedures*. You must establish, maintain, and follow written procedures for the control of distribution of PET drug products shipped from the PET production facility to ensure that the method of shipping chosen will not adversely affect the identity, purity, or quality of the PET drug product.

(b) *Distribution records*. 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) *Written complaint procedures*. You must develop and follow written procedures for the receipt and handling of all complaints concerning a PET drug product.

(b) *Complaint review*. The procedures must include review by a designated person of any complaint involving the possible failure of a PET drug product to meet any of its specifications and an investigation to determine the cause of the failure.

(c) *Complaint records*. 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 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 followup.

(d) *Returned products*. 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) *Record availability*. Records must be maintained at the PET production facility or another location that is reasonably accessible to responsible officials of the production facility and to employees of FDA designated to perform inspections.

(b) *Record quality*. 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.

(c) *Record retention period*. 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, including conditional final release, of a PET drug product.

Dated: September 1, 2005.

Jeffrey Shuren,

Assistant Commissioner for Policy.

[FR Doc. 05–18510 Filed 9–15–05; 8:45 am]

BILLING CODE 4160–01–S

ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 52

[R05–OAR–2005–WI–0003; FRL–7970–7]

Approval and Promulgation of Implementation Plans; Wisconsin; General and Registration Permit Programs

AGENCY: Environmental Protection Agency (EPA).

ACTION: Proposed rule.

SUMMARY: EPA is proposing to approve revisions to the Wisconsin State Implementation Plan (SIP) submitted by the State of Wisconsin on July 28, 2005. These revisions include General and Registration permit programs that provide for the issuance of general and registration permits as part of the State's construction permit and operation permit programs. In addition, these permit programs may include the regulation of hazardous air pollutants (HAPs) which may be regulated under section 112 of the Clean Air Act (the Act). Thus, EPA is also proposing approval of Wisconsin's general and registration permit program under section 112(l) of the Act.

These SIP revisions also contain changes to definitions related to Wisconsin's air permit program, as well as a minor technical change to provide correct references to the recently updated chapter NR 445, which was inadvertently omitted in the processing of that rule package. Additionally, these revisions clarify an existing construction permit exemption and operation permit exemption for certain grain storage and drying operations. This clarification is necessary to ensure that column dryers and rack dryers are included in the exemption criteria.

DATES: Written comments must be received on or before October 20, 2005.

ADDRESSES: Submit comments, identified by Regional Material in EDocket (RME) ID No. R05–OAR–2005–WI–0003, by one of the following methods:

Federal eRulemaking Portal: *http://www.regulations.gov*. Follow the on-line instructions for submitting comments.

Agency Web site: *http://docket.epa.gov/rmepub/*. RME, EPA's electronic public docket and comments system, is EPA's preferred method for receiving comments. Once in the system, select ''quick search,'' then key in the appropriate RME Docket identification number. Follow the on-line instructions for submitting comments.

E-mail: *blakley.pamela@epa.gov*.

Fax: (312) 886–5824.

Mail: You may send written comments to: Pamela Blakley, Chief, Air Permit Section, (AR–18J), U.S. Environmental Protection Agency, Region 5, 77 West Jackson Boulevard, Chicago, Illinois 60604.

Hand Delivery or Courier: Deliver your comments to: Pamela Blakley, Chief, Air Permit Section, (AR–18J), U.S. Environmental Protection Agency, Region 5, 77 West Jackson Boulevard, 18th floor, Chicago, Illinois 60604. Such deliveries are only accepted during the Regional Office's normal hours of operation. The Regional Office's official hours of business are Monday through Friday, 8:30 a.m. to 4:30 p.m. excluding Federal holidays.

Instructions: Direct your comments to RME ID No. R05–OAR–2005–WI–0003. EPA's policy is that all comments received will be included in the public docket without change and may be made available online at *http://docket.epa.gov/rmepub/*, including any personal information provided, unless the comment includes information claimed to be Confidential Business Information (CBI) or other information whose disclosure is restricted by statute. Do not submit information that you consider to be CBI or otherwise protected through RME, regulations.gov, or e-mail. The EPA RME website and the federal regulations.gov Web site are ''anonymous access'' systems, which means EPA will not know your identity or contact information unless you provide it in the body of your comment. If you send an e-mail comment directly to EPA without going through RME or