(2) *Airworthy Product:* For any requirement in this AD to obtain corrective actions from a manufacturer or other source, use these actions if they are FAA-approved. Corrective actions are considered FAA-approved if they are approved by the State of Design Authority (or their delegated agent). You are required to assure the product is airworthy before it is returned to service.

(3) *Reporting Requirements:* For any reporting requirement in this AD, under the provisions of the Paperwork Reduction Act (44 U.S.C. 3501 *et seq.*), the Office of Management and Budget (OMB) has approved the information collection requirements and has assigned OMB Control Number 2120–0056.

Related Information

(i) Refer to MCAI European Aviation Safety Agency Airworthiness Directive 2009–0237–E, dated October 30, 2009; and the service information specified in Table 2 of this AD; for related information.

TABLE 2—RELATED SERVICE INFORMATION

Airbus AOT—	Dated—
A330–35A3026	October 26, 2009.
A340–35A4027	October 26, 2009.
A340–35A5019	October 26, 2009.

Material Incorporated by Reference

(j) You must use the applicable service information contained in Table 3 of this AD to do the actions required by this AD, unless the AD specifies otherwise. (Only the first page of these documents contains the document number, revision level, and date; no other page of these documents contains this information.)

TABLE 3—MATERIAL INCORPORATED BY REFERENCE

Airbus AOT—	Dated—
A330–35A3026	October 26, 2009.
A340–35A4027	October 26, 2009.
A340–35A5019	October 26, 2009.

(1) The Director of the Federal Register approved the incorporation by reference of this service information under 5 U.S.C. 552(a) and 1 CFR part 51.

(2) For service information identified in this AD, contact Airbus SAS—Airworthiness Office—EAL, 1 Rond Point Maurice Bellonte, 31707 Blagnac Cedex, France; telephone +33 5 61 93 36 96; fax +33 5 61 93 45 80; e-mail: *airworthiness.A330-A340@airbus.com*; Internet *http://www.airbus.com*.

(3) You may review copies of the service information at the FAA, Transport Airplane Directorate, 1601 Lind Avenue, SW., Renton, Washington. For information on the availability of this material at the FAA, call 425–227–1221 or 425–227–1152.

(4) You may also review copies of the service information that is incorporated by reference 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*.

Issued in Renton, Washington, on November 30, 2009.

Michael J. Kaszycki,

Acting Manager, Transport Airplane Directorate, Aircraft Certification Service.

[FR Doc. E9–29378 Filed 12–9–09; 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. FDA–2004–N–0449] (formerly Docket No. 2004N–0439)

Current Good Manufacturing Practice for Positron Emission Tomography Drugs

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing regulations on current good manufacturing practice (CGMP) for positron emission tomography (PET) drugs. The regulations are intended to ensure that PET drugs meet the requirements of the Federal Food, Drug, and Cosmetic Act (the act) regarding safety, identity, strength, quality, and purity. In this final rule, we are establishing CGMP regulations for approved PET drugs. For investigational and research PET drugs, the final rule states that the requirement to follow CGMP may be met by complying with these regulations or by producing PET drugs in accordance with the United States Pharmacopeia (USP) general chapter on compounding PET radiopharmaceuticals. We are establishing these CGMP requirements for 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**, we are announcing the availability of a guidance entitled ''PET Drugs—Current Good Manufacturing Practice (CGMP).''

DATES: This regulation is effective December 12, 2011. The incorporation by reference of a certain publication listed in the rule is approved by the Director of the Federal Register as of December 12, 2011.

FOR FURTHER INFORMATION CONTACT: Brenda Uratani, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20993–0002, 1–240–328–7621, e-mail: *Brenda.Uratani@fda.hhs.gov*.

SUPPLEMENTARY INFORMATION:

Table of Contents

I. Introduction

We are adding to our regulations new part 212 (21 CFR part 212) to establish CGMP requirements for PET drugs in accordance with section 121 of the Modernization Act (Public Law 105–115).

A. Background

In the **Federal Register** of September 20, 2005 (70 FR 55038) (2005 proposed

rule), we published a proposed rule to establish CGMP requirements for PET drugs. PET is a medical imaging modality involving the use of a unique type of radiopharmaceutical drug product. The majority of PET drugs are injected intravenously into patients for diagnostic purposes. Section 121(c)(1)(A) of the Modernization Act directed us to establish appropriate approval procedures and CGMP requirements for PET drugs. During our development of these PET drug CGMP requirements and approval procedures, we were to take due account of any relevant differences between not-for-profit institutions that compound PET drugs for their patients and commercial manufacturers of PET drugs and to consult with patient advocacy groups, professional associations, manufacturers, and physicians and scientists who make or use PET drugs (section 121(c)(1)(B) of the Modernization Act). In the preamble to the 2005 proposal, we described the steps we took and the groups we consulted while developing the proposed regulations on PET drug CGMP. We refer readers to the preamble of the 2005 proposal for details on these events, information on the unique nature of PET drugs, and our conclusions regarding the current status of PET drug production in the United States.

B. The Proposed Rule

In the proposed rule, we stated that the proposed CGMP requirements would contain the minimum standards needed for PET drug production at all types of PET production facilities. We further stated that the proposed CGMP regulations were designed 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 drugs differed in many significant ways from the CGMP requirements for non-PET drugs found in our regulations in parts 210 and 211 (21 CFR parts 210 and 211). The proposed PET CGMP requirements included differences concerning personnel; aseptic processing; quality control of components; self-verification of production steps; same-person oversight of production, batch record review, and authorization of product release; and labeling requirements.

C. Changes to the Proposed Rule

We received 11 comments on the proposed rule, which we address in section III of this document. As a result of the comments, and upon further review on our own initiative, we have made several changes to the proposed PET CGMP requirements, including the following:

- We have substituted the term ''quality assurance'' for ''quality control'' and revised the definition.
- We have clarified that the CGMP requirements followed for the study of PET drugs under an investigational new drug application (IND) or under the review of a Radioactive Drug Research Committee (RDRC) (which reviews and approves the use of radioactive drugs for certain limited research purposes in accordance with 21 CFR 361.1) may be either the regulations in part 212 or the standards in Chapter 823, ''Radiopharmaceuticals for Positron Emission Tomography—Compounding'' of the 32d ed. of the USP (2009) (USP 32).
- We have simplified the requirement for identification of a sample received for laboratory testing.
- We have provided more flexibility in method for determining that each batch of a PET drug product conforms to specifications before final release.
- We revised the circumstances under which conditional final release may be acceptable.

When we published the proposed rule on PET CGMP, we also made available a revised draft guidance on CGMP for PET drugs (70 FR 55145, September 20, 2005). Elsewhere in this issue of the **Federal Register**, we are announcing the availability of a guidance entitled ''PET Drugs—Current Good Manufacturing Practice (CGMP)'' to further assist PET production facilities in complying with the requirements in the final rule.

II. Unique Aspects of the PET CGMP Regulations

The final rule establishes several differences between CGMP requirements for PET drugs and CGMP requirements for other drugs in parts 210 and 211. Included among these differences are the following:

- 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 assurance 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;
- Greater flexibility in approaches to determining whether PET drug products conform to their specifications;
- Specialized quality assurance requirements for PET drugs produced in multiple sub-batches; and
- Simplified labeling requirements consistent with the scope and complexity of operations.

III. Comments on the Proposed Rule

We received 11 comments on the proposed rule, including 6 from PET drug producers, 3 from industry associations, 1 from a consultant, and 1 from the USP. A summary of the comments received and our responses follow.

A. General Comments

(Comment 1) Several comments recommended that the title of the proposed rule be changed to ''Current Good Manufacturing Practice for Positron Emission Tomography Drug Products.'' The comments stated that the draft guidance title refers to ''PET Drug Products,'' and the comments maintained that the focus of the rule is on drug products.

(Response) We do not agree with the comments. Section 121(c)(1)(A)(ii) of the Modernization Act requires us to develop appropriate CGMP requirements for PET ''drugs,'' rather than PET ''drug products.'' The definition of ''compounded positron emission tomography drug'' in section 121(a) of the Modernization Act (codified at section 201(ii) of the act (21 U.S.C. 321(ii))), encompasses both a PET drug product (i.e., a PET drug in finished dosage form) and the active pharmaceutical ingredient (API) that is incorporated into a PET drug product and enables the product to perform its diagnostic function (e.g., the 2-deoxy-2-[18F]fluoro-D-glucose in an FDG F 18 injection drug product). Thus, the PET CGMP requirements are applicable to the production of a PET API as well as the PET drug product containing that API.

To clarify that the PET CGMP regulations apply to PET drugs, not solely to PET drug products, we have made several revisions to the proposed rule. To the definition of ''PET drug'' in § 212.1, we have added the following statement: '''PET drug' includes a 'PET drug product' as defined in this

section.'' We also have revised the definition of ''PET drug product'' in § 212.1 to state as follows: ''*PET drug product* means a finished dosage form of a PET drug, whether or not in association with one or more other ingredients.'' We have revised §§ 212.2 and 212.5 to make clear that the PET CGMP requirements apply to PET drugs (not only to PET drug products), and, where appropriate, we have revised other sections of part 212 accordingly. For those provisions in part 212 that are intended to apply only to finished dosage forms of PET drugs, the term ''PET drug product'' is used.

(Comment 2) As noted in the response to the previous comment, section 121(a) of the Modernization Act added a definition of ''compounded positron emission tomography drug'' to the act as section 201(ii). One comment stated that although section 121(a) of the Modernization Act recognizes that PET drugs can be compounded and that compounding can occur by or on the order of a practitioner who is licensed by a State to compound or order compounding for a PET drug, the proposed rule focuses primarily on manufacturing and does not appear to recognize the role of professional practitioners in the practice of medicine and pharmacy. The comment stated that the agency seems to have determined that production of a PET drug is exclusively an issue of regulatory adherence, apparently unintentionally removing the standard of professional responsibility traditionally established for the practice of medicine and pharmacy, and treating all producers of PET drugs as manufacturers. The comment referred to the draft guidance, which states that: (1) Production of a PET drug includes all operations to the point of final release of a finished dosage form, and (2) after a PET drug product is received by the receiving facility, subsequent dispensing of a patient-specific dose and use of the PET drug is regarded as part of the practice of medicine and pharmacy. The comment maintained that the rule and the guidance should state that they only apply to noncompounded PET drugs and that the compounding of PET drugs will continue to be subject to the requirements of the various State boards of medicine and pharmacy as well as the PET compounding standards and monographs of the USP.

(Response) We do not agree with the comment that the proposed rule did not recognize the practice of medicine and pharmacy with respect to PET drugs. The proposed rule did not include regulations on the administration or dispensing of PET drug products. The proposed rule defined ''production'' of a PET drug as the manufacturing, compounding, processing, packaging, labeling, reprocessing, repacking, relabeling, and testing of a PET drug. As the comment noted, the draft guidance stated that production includes all operations to the point of final release of a finished dosage form, and use of a PET drug product after receipt by a receiving facility generally is regarded as the practice of medicine and pharmacy.

The Modernization Act does not require separate regulations for compounded PET drugs and noncompounded PET drugs. Section 121(b) of the Modernization Act states that, until after the later of 4 years after the date of enactment of the Modernization Act or 2 years after the agency establishes approval procedures and CGMP requirements for PET drugs, a compounded PET drug is not adulterated if it is compounded, processed, packed, or held in conformity with the PET compounding standards and official monographs of the USP. Thus, after the later of the two specified times, the CGMP requirements that FDA will have established for PET drugs will apply to compounded PET drugs. The fact that some production or ''compounding'' of PET drugs is performed by physicians, including some academicians and researchers at facilities located in universities and other not-for-profit institutions, does not remove such production from the scope of the PET CGMP regulations. Consistent with the Modernization Act, the final rule ensures that the production of compounded PET drugs is subject to the CGMP regulations while permitting the dispensing and administration of PET drug products in accordance with State regulation of the practice of medicine and pharmacy.

(Comment 3) One comment questioned whether new drug applications (NDAs) and abbreviated new drug applications (ANDAs) are needed or realistic for very short lived PET drugs that logistically require in-house preparation, such as those labeled with O–15. The comment maintained that the preparation of these drugs falls more closely under the definition of compounding than manufacturing because their extremely short half-lives preclude marketing and distribution. The comment stated that these short half-life PET drugs are individually compounded onsite, one dose at a time, for specific individual patients, which means that the drugs have no commercial potential and thus are not marketed.

(Response) As stated in our response to comment 2, under the Modernization Act, there is no difference between compounding PET drugs and producing PET drugs. Having a very short half-life might mean that a PET drug could not be distributed to a facility outside of the one in which it was produced, but the product could still be produced, released for use, and administered to patients within the same facility. It is just as important that these PET drugs be produced under approved applications—and be subject to CGMP—as it is for PET drugs that are produced and distributed to other facilities for subsequent administration to patients.

(Comment 4) One comment stated that although section 121(c)(1)(B) of the Modernization Act directs FDA to take due account of the relevant differences between not-for-profit institutions that compound PET drugs and commercial manufacturers of PET drugs, the agency concluded that profit or not-for-profit status does not have a significant bearing on the quality of PET drugs that are produced and distributed. The comment stated that we seem to have concluded that the only way to regulate the production of PET drugs is to require an NDA or ANDA. The comment stated that our decisions on how to enforce the Modernization Act appear to have been greatly influenced by the commercialization of PET drugs and the fact that many PET drugs and studies are reimbursed by the government and private insurance payors. The comment stated that although we had simplified the approval process for 3 PET drugs (fludeoxyglucose (FDG) F 18 injection, ammonia N 13 injection, and sodium fluoride F 18 injection) for specified indications in the notice published in the March 10, 2000, issue of the **Federal Register** (65 FR 12999) (March 2000 Notice), there are other PET drugs in use and the USP contains monographs for 12 PET drugs. The comment maintained that it will be an almost insurmountable hurdle for many facilities to submit NDAs or ANDAs for the PET drugs for which FDA has not developed a template, guidance, and instructions for preparing marketing applications. The comment added that approved PET drug products might have patent and market exclusivity protection, and it would be unlikely that commercial PET facilities would invite competition.

(Response) The Modernization Act does not leave the manner in which PET drugs are to be regulated completely to FDA's discretion. Rather, in section 121(c)(1)(A)(i), Congress directed the agency to develop ''appropriate procedures for the approval of positron emission tomography drugs *pursuant to*

section 505 of the [act] (21 U.S.C. 355)'' (emphasis added). Section 505 of the act (21 U.S.C. 355) contains the provisions on new drugs, including provisions on NDAs and ANDAs. To the extent that increased commercialization of PET drugs has affected the size, scope, and complexity of PET drug production operations, the PET CGMP regulations indirectly reflect this market reality. However, as we stated in the proposed rule, not-for-profit versus for-profit status does not (and should not) have a significant bearing on the quality of PET drugs produced or the facilities and procedures needed to ensure product quality. Thus, our approach to the regulation of PET drugs has been shaped largely by these statutory and product quality imperatives, rather than commercialization or reimbursement concerns.

Regarding approval procedures for PET drugs, in the proposed rule to establish regulations on the evaluation and approval of diagnostic radiopharmaceuticals (63 FR 28301, May 22, 1998), we stated that although we expected the standards for determining the safety and effectiveness of diagnostic radiopharmaceuticals set forth in the proposed rule to apply to PET drugs, we would address that issue when we published our proposal on PET drugs. On May 17, 1999 (64 FR 26657), we published the final rule establishing regulations on the review and approval of diagnostic radiopharmaceutical drugs in part 315 (21 CFR part 315) and diagnostic radiopharmaceutical biologics in part 601 (21 CFR part 601) (§§ 601.30 through 601.35). These regulations complement and clarify the regulations on the approval of drugs and biologics in part 314 (21 CFR part 314) and part 601, respectively.

Part 315 provides considerable detail on what is needed to obtain approval of an application for a diagnostic radiopharmaceutical. Part 315 includes provisions on the following:

- General factors relating to the safety and effectiveness of diagnostic radiopharmaceuticals;
- The types of indications for which approval might be sought and the evidence needed to support those indications; and
- The factors that we consider in making a safety assessment of a diagnostic radiopharmaceutical and the types of information needed to demonstrate that a product is safe.

In addition, we have issued three guidance documents to assist developers of medical imaging drug and biological products in planning and coordinating their clinical investigations and preparing and submitting INDs and marketing applications (69 FR 34683, June 22, 2004). These guidances on ''Developing Medical Imaging Drug and Biological Products'' are as follows: ''Part 1: Conducting Safety Assessments;'' ''Part 2: Clinical Indications;'' and ''Part 3: Design, Analysis, and Interpretation of Clinical Studies.''

In the March 2000 Notice, we declared FDG F 18 injection, ammonia N 13 injection, and sodium fluoride F 18 injection to be safe and effective for certain indications when produced under conditions specified in approved applications. We took this action after reviewing the published literature on these drugs and indications and after presenting our preliminary findings at public meetings and before the Medical Imaging Drugs Advisory Committee. We issued the March 2000 Notice to help make it easier for all PET drug producers to obtain marketing approval for these commonly used PET drugs. The March 2000 Notice, along with a draft guidance document entitled ''PET Drug Applications—Content and Format for NDAs and ANDAs'' (65 FR 13010, March 10, 2000), which we intend to finalize in the near future, provides considerable assistance to PET drug producers in submitting applications for these commonly used PET drug products.

In the March 2000 Notice, we noted that, in a future issue of the **Federal Register**, we intended to state our approach to applications for approval of other PET drugs and new indications for approved drugs in accordance with the Modernization Act. After considering this issue, we conclude that it is appropriate to apply part 315 to the review and approval of new PET drugs and new indications for approved PET drugs under part 314. We believe that the use of PET drugs raises safety and effectiveness concerns that are comparable to those posed by other diagnostic radiopharmaceuticals. Although PET drugs differ in some ways from other diagnostic radiopharmaceuticals, such as in their often very short half-lives and limited distribution environment, we find that these differences are not so pronounced that they necessitate the establishment of separate approval regulations. Therefore, we conclude that parts 314 and 315 of the regulations constitute the appropriate approval procedures for PET drugs in accordance with section 121(c)(1)(A)(i) of the Modernization Act.

We realize that submitting marketing applications for PET drugs under parts 314 and 315 will require considerably more resources than are needed to submit applications for the PET drug products and indications listed in the March 2000 Notice. However, the agency lacks the resources to conduct literature reviews to determine the safety and effectiveness of all PET drugs and indications that might be used in the future. We believe that the guidances on ''Developing Medical Imaging Drug and Biological Products'' will greatly assist PET drug producers in investigating and seeking approval of new PET drugs and new indications for existing drugs in accordance with parts 314 and 315. We believe that these guidances will lessen the burden of PET drug producers in obtaining approval of new products.

As the comment noted, we acknowledge in the March 2000 Notice that PET drugs that we have approved might be protected from competition by patents, or by marketing exclusivity granted by us at the time of approval. We agree with the comment that these factors could have an effect on the availability of certain PET drugs. However, because patent and exclusivity rights are protected by statute, revising those rights would require Congressional action.

(Comment 5) One comment stated that the proposed rule failed to acknowledge that the size, scope, and complexity of production operations that lead to CGMP differences are also an important reflection of differences between not-for-profit and commercial institutions. The comment claimed that the rule might compel not-for-profit hospitals and research institutions to divert resources from research, health care delivery, and patient services to meet CGMP compliance obligations that are not grounded in clinical or safety considerations. In particular, the comment stated that subjecting hospitals and research institutions to the same inspection regime as large commercial producers would be unduly onerous. The comment stated that most facilities in hospitals and research institutions produce only limited doses of PET drugs for their own clinical use, they do not profit from such production, and they may lack the resources to satisfy FDA inspection requirements. The comment welcomed the opportunity to assist the agency in developing inspection guidelines that would ensure that the CGMP requirements and enforcement strategies take due account of any relevant differences between not-for-profit and for-profit institutions. In particular, the comment stated that, as a matter of enforcement discretion and practical implementation, we should only inspect not-for-profit facilities that produce PET

drugs for their own clinical use when we have cause to suspect that drug safety or quality has been compromised.

(Response) As we stated in the proposed rule, although there are some differences between not-for-profit and commercial institutions, there is some overlap between the two, including when for-profit entities manage the production of PET drugs within not-for-profit institutions. We concluded that the principal factors influencing production and CGMP differences among PET drug producers are the size, scope, and complexity of PET drug operations. We designed the CGMP regulations with these factors in mind, rather than trying to establish different CGMP requirements for several different kinds of producers. We believe that the CGMP regulations contain the minimum requirements needed to ensure the safety, identity, strength, quality, and purity of all PET drugs, regardless of where they are produced. Although we recognize that PET drug producers will incur costs in coming into compliance with the PET CGMPs (see the analysis of economic impacts in section IV of this document), we believe that CGMP expenditures by not-for-profit institutions and commercial producers will benefit patients who receive PET drugs.

We appreciate the comment's concern about the impact of inspections on PET drug producers. In the preamble to the proposed rule, we stated that, for PET drugs studied under an IND and PET drugs produced for research under the review of an RDRC, we generally would conduct inspections only on a for-cause basis. For preapproval inspections and inspections of marketed drugs, we will consider such factors as the size, scope, and complexity of operations in establishing our inspectional approach. We would expect that because many hospitals and research institutions have smaller operations, the impact on operations that those institutions might experience due to an inspection would be less than the impact experienced by a commercial producer with significantly larger operations. In any case, we will provide training to agency inspectors so that they conduct inspections in a manner that is consistent with the regulations yet takes into account relevant differences among PET drug producers.

(Comment 6) One comment expressed support for the incorporation into the proposed rule of principles and definitions in the USP general chapter on compounding PET radiopharmaceuticals.

(Response) As we stated in the proposed rule, the fact that Chapter 823 reflects the views of the PET community and the agency on how to properly produce PET drugs makes it appropriate to incorporate principles and concepts from Chapter 823 into the CGMP requirements. In addition, as discussed in response to comment 25, under § 212.5(b) of the final rule, for investigational and research PET drugs, the requirement under the act to follow CGMP is met by complying with part 212 or by producing the drugs in accordance with Chapter 823 of the USP's 32d ed. (the current (2009) edition of the USP).

(Comment 7) One comment stated that, although many regulations require drug manufacturers to include pediatric data with their NDA submissions, PET drugs by definition are for metabolic and/or diagnostic studies and do not elicit pharmacologic effect. The comment stated that if the metabolic pathway being studied is functional in pediatric patients, it stands to reason that the PET drug will appropriately provide the diagnostic data needed. The comment maintained that if the pediatric regulations are allowed to impact the PET CGMP regulations, many children will be unnecessarily exposed to radiation and NDA submissions will be inappropriately delayed, without scientific benefit, for the sole purpose of meeting the pediatric regulations. Therefore, the comment recommended that part 212 be exempted from all regulations that require pediatric data collection or submission for primary or continued approval.

(Response) The question of the application of the statutory and regulatory provisions on pediatric study requirements to PET drugs is beyond the scope of this rulemaking.

B. Scope of Part 211 (Proposed § 211.1)

The proposed rule included revisions to parts 210 and 211 to exclude PET drugs from the scope of CGMP for the manufacturing, processing, packing, or holding of drugs and CGMP for finished pharmaceuticals.

(Comment 8) One comment expressed support for the exclusion of PET drugs from the scope of the requirements in parts 210 and 211.

(Response) Exclusion of PET drugs from the scope of parts 210 and 211 is necessary and appropriate in light of the establishment of CGMP requirements for PET drug products in accordance with the Modernization Act.

(Comment 9) One comment stated that FDA inspectors will need retraining to make the exclusion of PET drugs from parts 210 and 211 clear in practice.

(Response) We will provide FDA field offices with adequate training regarding the new CGMP regulations for PET drugs in part 212 so that agency officials can conduct appropriate inspections to determine compliance with these regulations.

C. Definitions (Proposed § 212.1)

1. Active Pharmaceutical Ingredient

In the proposed rule, ''active pharmaceutical ingredient'' was defined as a substance that is intended for incorporation into a finished PET drug product and is intended to furnish pharmacological activity or other direct effect in the diagnosis 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.

(Comment 10) Several comments stated that PET drugs by their nature as diagnostic drugs should not elicit a pharmacological effect, so they recommended deleting ''pharmacological activity'' from the definition. One comment specifically recommended substituting ''to furnish the physiological pathway'' for ''to furnish pharmacological activity or other direct effect.''

(Response) We do not agree with the comments. Although PET drugs as defined in these regulations are intended for diagnostic use and are not intended to provide a pharmacological effect, many PET drugs provide their diagnostic effect by binding to receptors, which is a type of pharmacological activity. In addition, the term ''physiological pathway'' would not be appropriate because some PET drugs may not actually furnish details of the physiological pathway. Therefore, we have not changed the definition of active pharmaceutical ingredient.

(Comment 11) Two comments stated that we should add ''treatment'' of a disease to the definition of active pharmaceutical ingredient because a PET drug may be used for tumor therapy.

(Response) We do not agree with the comment. Under section 121(a) of the Modernization Act, a ''compounded positron emission tomography drug'' is a drug that ''exhibits spontaneous disintegration of unstable nuclei by the emission of positrons and *is used for the purpose of providing dual photon emission tomographic diagnostic images*'' (codified as section 201(ii)(1)(A) of the act) (emphasis added). This wording in the definition means that the provisions of the Modernization Act concerning PET drugs, including the requirement that

we establish appropriate CGMP requirements for PET drugs, do not apply to PET drugs used for therapeutic purposes. Therefore, it would not be appropriate to define active pharmaceutical ingredient as including use of the substance in the treatment of a disease.

(Comment 12) One comment expressed support for the exclusion of intermediates or chemical precursors used in the synthesis and production of PET drugs from the definition of active pharmaceutical ingredient. The comment stated that proposed § 212.40(c)(1)(i) clarified that finished product testing and reliance on supplier certificates of analysis was appropriate to ensure that the correct components had been used.

(Response) Although intermediates are excluded from the definition of active pharmaceutical ingredient, we wish to make clear that intermediates, as components of PET drugs, are subject to the PET CGMP regulations (see, e.g., § 212.40 on control of components, containers, and closures).

2. Master Production and Control Record

We proposed to define ''master production and control record'' as a compilation of records containing the procedures and specifications for the production of a PET drug.

(Comment 13) Three comments recommended changes to the proposed definition. One comment stated that it inadequately describes the relationship of the master formula and batch sheet as used in PET drug production; according to the comment, the batch record is the documented activity recorded as the result of following the master formula. One comment stated that the master production and control record should be a detailed step-by-step instruction set, while the input and output information from the production batch is recorded in the batch record. Both of these comments recommended substituting the term ''control procedure'' for ''control record.'' One comment stated that to more accurately reflect that batch records need not be exact copies of the master production and control document, the term ''control document'' should be substituted for ''control record'' and the definition should be changed to ''a compilation of instructions containing the procedures for the production of a PET drug product and specifications for the product.''

(Response) We do not agree that it is appropriate to change the term ''control record'' because this is a standard term used in the production of drugs. However, we agree that it is appropriate to change the definition of master production and control record to a compilation of instructions (rather than records) containing the procedures and specifications for the production of a PET drug, and we have revised the definition accordingly.

3. PET Drug

We proposed 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 specifically 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. As stated in the proposed rule, this definition closely parallels the definition of PET drug in section 121(a) of the Modernization Act (codified as section 201(ii) of the act).

As stated in our response to comment 1, we have added the statement '''PET drug' includes a 'PET drug product' as defined in this section'' to the definition of ''PET drug'' in § 212.1.

(Comment 14) Two comments stated that because a PET drug may also be used for tumor therapy, the definition should state that a PET drug is used for providing diagnostic images or therapeutic procedures.

(Response) As stated in our response to comment 11, the provisions of the Modernization Act concerning PET drugs do not apply to PET drugs used for therapeutic purposes. Therefore, it would not be appropriate to define PET drug as including use of the drug for therapeutic purposes.

(Comment 15) Several comments addressed the second sentence of the definition of PET drug, which lists certain items that are included in the definition. Two comments stated that the second sentence of the definition is inaccurate within the practical and technical meaning of a drug and, specifically, a PET drug. One comment stated that the definition seems overly broad in that it includes both components and equipment used to produce the PET drug. Two comments stated that a PET drug product does not include the components of a PET drug listed in the second sentence of the definition, necessitating a change to the definition of ''PET drug'' or ''PET drug product.'' One comment stated that generators, accelerators, electronic synthesizers, and computer programs should be deleted from the definition because they are not PET drugs but ancillary items.

(Response) Section 201(ii)(2) of the act states that a compounded 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 such a drug.'' Therefore, it is appropriate that the definition of ''PET drug'' in the CGMP regulations for PET drugs include these items. However, because a ''PET drug product'' is defined as ''a finished dosage form of a PET drug,'' it is not necessary that the definition restate the list of items set forth in the definition of ''PET drug.''

(Comment 16) Two comments stated that a generator system that produces a PET radionuclide from the decay of a longer half-lived parent isotope should be regulated under the CGMP requirements in part 211.

(Response) The generator system described in the comments is a nuclide generator under the definition of PET drug in section 201(ii)(2) of the act. Therefore, such generator systems are included in the definition of PET drug in § 212.1 and are subject to the CGMP requirements in part 212. FDA has approved an NDA for a PET drug containing a generator (rubidium chloride RB-82 generator).

(Comment 17) One comment stated that although liquid target material for PET production facilities seems to fall under the proposed definition of PET drug, the comment did not believe that we intended to regulate producers of this material under part 212.

(Response) Target material is included in the definition of PET drug in section 201(ii)(2) of the act. Therefore, it is appropriate to include target material in the definition of PET drug in § 212.1. Target material is thus subject to the PET CGMP requirements in part 212, including the provisions on components of PET drugs in § 212.40. However, with respect to the manufacture of target material that is intended to be used as a component of a PET drug, we intend to exercise our enforcement discretion by not requiring compliance with part 212.

(Comment 18) One comment stated that an alternative to the proposed definition would be to develop consistency with part 315 for diagnostic radiopharmaceuticals because PET drugs are radiopharmaceuticals. The comment stated that this would help maintain clarity of language when discussing all radiopharmaceuticals and eliminate sources of confusion in the proposed definition of PET drug.

(Response) Section 315.2 of the regulations defines ''diagnostic radiopharmaceutical'' as an article that is intended for use in the diagnosis or monitoring of a disease or a manifestation of a disease in humans and that exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons, or any nonradioactive reagent kit or nuclide generator that is intended to be used in the preparation of such an article. Because we are implementing these CGMP regulations for PET drugs in accordance with section 121 of the Modernization Act, it is appropriate that the definition of PET drug in § 212.1 reflect the definition in the Modernization Act (section 201(ii) of the act). We believe that the definition of PET drug in § 212.1 is sufficiently consistent with the definition of diagnostic radiopharmaceutical in § 315.2 that it is unlikely to cause confusion.

(Comment 19) One comment stated that ''PET drug'' and ''PET drug product'' are used somewhat interchangeably in the proposed rule. For example, the comment noted that although proposed § 212.5(a) states that the regulations apply to PET drug products, the title of § 212.40 refers to ''PET drugs.''

(Response) As stated in our response to comment 1, we have revised the proposed rule to clarify that the PET CGMP regulations apply to PET drugs, which include PET drug products (i.e., finished dosage forms of PET drugs). Where a provision is intended to apply only to finished dosage forms of PET drugs (e.g., § 212.61 on stability, § 212.80 on labeling and packaging), the term ''PET drug product'' is used. Therefore, the title of § 212.40 continues to refer to ''PET drugs.'' However, provisions in § 212.40 refer to ''drug product'' containers and closures and to finished-product testing of a ''PET drug product'' because these provisions are applicable only to finished dosage forms of PET drugs.

4. PET Drug Product

We proposed 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.

As stated in our response to comment 1, we have redefined ''PET drug product'' as a finished dosage form of a PET drug, whether or not in association with one or more other ingredients.

(Comment 20) One comment stated that the definition of PET drug product should be revised to ''a finished dosage form suitable for administration to humans.'' The comment further stated that for a PET drug product to be administered intravenously, it should comply with the sterility requirements for parenterals.

(Response) We do not believe that it is necessary to refer specifically to humans in the definition of PET drug product because § 212.2 states that CGMP for PET drugs is the minimum requirements for the methods to be used in, and the facilities and controls used for, the production, quality assurance, holding, or distribution of PET drugs intended for human use. With respect to CGMP sterility requirements, all injectable PET drugs must meet the requirements for sterility testing in § 212.70(e).

5. PET Production Facility

We proposed to define ''PET production facility'' as a facility that is engaged in the production of a PET drug.

(Comment 21) Two comments stated that the definition of PET production facility does not accurately depict the actual function of the facility. The comments stated that the definition could be interpreted to include a facility for the production of PET scanners or for the acquisition of PET images. The comments stated that the term ''PET drug production facility'' would more precisely reflect the proposed definition.

(Response) We agree with the comments and have substituted ''PET drug production facility'' for ''PET production facility.''

6. Quality Control

We proposed to define ''quality control'' as 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.

(Comment 22) Several comments recommended substituting ''ensuring'' for ''maintaining'' in the definition of quality control. One comment stated that quality control activities are more commonly defined as intended to ensure quality rather than maintain quality.

(Response) We agree with the comment and have revised the definition accordingly. In addition, on our own initiative we have replaced the term ''quality control'' with ''quality assurance.'' We believe that the term quality assurance more accurately reflects a system that is intended to ensure the quality of active ingredients, components, and other elements of PET drug production through the use of various procedures, tests, analytical methods, and acceptance criteria. Moreover, we believe that this change is consistent with subpart C, ''Quality Assurance,'' of the PET CGMP regulations, and specifically with § 212.20(e), which requires PET drug producers to establish and follow written quality assurance procedures.

7. Sub-batch

(Comment 23) Three comments recommended that § 212.1 include a definition of ''sub-batch,'' as defined in USP Chapter 823: ''A quantity of PET drug product having uniform character and quality, within specified limits, that is produced during one succession of multiple irradiations, using a given synthesis and/or purification operation.''

(Response) We agree with the comments and have included a definition of sub-batch in § 212.1, using the definition in USP Chapter 823 to which the comments referred.

D. Application (Proposed § 212.5)

Proposed § 212.5(a) stated part 212 applies only to the production, quality control, holding, and distribution of PET drug products. It further stated that any human drug product that does not meet the definition of a PET drug product must be manufactured in accordance with the CGMP requirements in parts 210 and 211. Proposed § 212.5(a) also stated that part 212 applies to all PET drug products for human use except for investigational and research PET drugs as described in § 212.5(b).

Proposed § 212.5(b) stated that the regulations in part 212 do not apply to investigational PET drugs or drug products for human use produced under an IND in accordance with part 312 and PET drugs or drug products produced with the approval of an RDRC in accordance with part 361. Proposed § 212.5(b) further stated that for such investigational and research PET drugs or drug products, the requirement under the act to follow CGMP is met by producing PET drugs or drug products in accordance with Chapter 823 of the 28th ed. of the USP, which was incorporated by reference in the proposed rule.

As stated in response to comment 1, we have revised § 212.5 to make clear that the PET CGMP requirements apply to PET drugs, not solely to PET drug products. Correspondingly, we have revised § 212.5(b) to state that for

''investigational PET drugs for human use produced under an IND in accordance with part 312'' and ''PET drugs produced with the approval of an RDRC in accordance with part 361,'' the requirement to follow CGMP is met by producing these drugs in accordance with Chapter 823 of the 32d ed. of the USP.

(Comment 24) One comment expressed support for the exclusion of PET drugs studied under an IND or RDRC review from the scope of the PET drug CGMP regulations. However, one comment stated that there is an understanding within the industry, based on experiences with preapproval inspections, that the agency expects that investigational drugs for Phase 3 clinical trials will be produced under CGMP conditions to link the drugs to production of market batches. Therefore, the comment requested that we clarify whether, under § 212.5(b), CGMP will apply to the production of PET drug products for Phase 3 trials.

(Response) Under the proposed rule, investigational and research PET drugs produced in accordance with USP Chapter 823 would be deemed to meet CGMP requirements. As we stated in the preamble to the proposed rule, we believe that it is appropriate to have more flexible CGMP requirements for these drugs during development. Because many PET drugs are produced under an IND or RDRC review and most PET drug producers are familiar with the standards in Chapter 823, adopting USP 32 Chapter 823 as an alternative standard for CGMP for investigational and research PET drugs should make it easier for PET drug producers to comply with the CGMP requirements.

Nevertheless, we agree with the comment that a PET drug producer intending to seek marketing approval for a PET drug or new indication should conduct Phase 3 studies on the drug in accordance with the PET CGMP requirements in part 212. Therefore, we have revised § 212.5(b) to state that for investigational and research PET drugs, the requirement under the act to follow CGMP is met by complying with part 212 or by producing PET drugs in accordance with USP 32 Chapter 823. This revised provision gives producers of investigational and research PET drugs the flexibility of choosing to follow the CGMP requirements in part 212 or meeting the standards in USP 32 Chapter 823, depending on the purposes of the investigation or research with the PET drug.

(Comment 25) One comment stated that because the USP is frequently updated, the regulations should not refer to a specific edition.

(Response) We do not agree with the comment. It would not be appropriate to permit future changes to Chapter 823 to be incorporated into part 212 without conducting notice and comment rulemaking. We believe that the current version of Chapter 823 (in the 32d ed. of the USP) contains appropriate CGMP standards for investigational and research PET drugs. If Chapter 823 is changed in the future, we will consider whether it is appropriate to issue a proposed rule to revise the PET CGMP regulations to incorporate the revisions to the chapter.

E. Personnel and Resources (Proposed § 212.10)

Proposed § 212.10 stated that a PET drug producer must have a sufficient number of personnel with the necessary education, background, training, and experience to perform their assigned functions. It further stated that a PET drug producer must have adequate resources, including facilities and equipment, to enable its personnel to perform their functions.

(Comment 26) One comment remarked that the discussion of proposed § 212.10 in the preamble of the proposed rule stated that 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 drugs or a facility producing larger amounts of a PET drug. The comment stated that because there are not likely to be any operations (commercial or noncommercial) that produce only one or two doses each day (or week), the statement unrealistically portrays a simple operation. The comment maintained that the draft guidance on PET CGMP (lines 226 through 230) more accurately defines a small operation as one that produces only one or two batches of a PET drug daily. The comment recommended that the wording in the introduction to the final rule be changed to be consistent with the draft guidance.

(Response) We agree with the comment that it is appropriate to characterize a small PET drug production operation as one that produces only one or two batches each day (or week) of a single PET drug, as stated in the final guidance. We note, however, that it is not unusual for a batch of a PET drug to consist of very few doses.

F. Production and Process Controls (Proposed § 212.50)

1. Master Production and Control Records

Proposed § 212.50(b)(1) through (b)(6) listed certain items of information that would be required in a master production and control record. These included, in proposed § 212.50(b)(6), a statement of acceptance criteria on radiochemical yield, i.e., the minimum percentage of yield beyond which investigation and corrective action are required.

(Comment 27) One comment recommended deletion of this requirement. The comment stated that radiochemical yields can have significant variations in a well-controlled PET manufacturing operation and that many factors can affect the yield. The comment maintained that radiochemical yield is not a significant predictor of product quality. According to the comment, discarding useful product and having to produce another lot based on arbitrary radiochemical yield increases radiation exposure without predicting product quality.

(Response) We do not agree with the comment. Although a low radiochemical yield would not necessarily require the rejection of a batch, low radiochemical yield can be a useful predictor of control of the production process for a PET drug. For example, a low radiochemical yield might result from a leak in the production system that introduces an extraneous substance, resulting in a contaminated product that might not be easily purified. Repeated occurrences of low radiochemical yield or a downward trend in radiochemical yield should prompt an investigation and, if necessary, corrective action. We have revised § 212.50(b)(6) to require a statement of action limits, rather than acceptance criteria, on radiochemical yield, because exceeding the radiochemical yield limits would require investigation and corrective action but not necessarily rejection of the batch.

2. Batch Production and Control Records

Proposed § 212.50(c)(1) to (c)(11) listed the items of information that must be included on a batch production and control record. These included, in proposed § 212.50(c)(6), the dates and time of production steps.

(Comment 28) One comment stated that recording the time of critical production steps is appropriate but recording the date and time of each step is not necessary. The comment stated

that the manufacture of a PET drug takes place over a few hours at most. The comment maintained that recording the date once on the batch record is sufficient unless production spans 2 days. The comment also recommended that recording the time be limited to critical steps, contending that doing so for all steps would de-emphasize critical steps.

(Response) We believe that it is appropriate to record the date of each production step on the batch production and control record. However, we agree with the comment that the time need only be recorded for each critical production step (e.g., start of irradiation, beginning and end of synthesis). Therefore, we have revised § 212.50(c)(6) to require inclusion of the dates of production steps and times of critical production steps.

G. Laboratory Controls (Proposed § 212.60)

Proposed § 212.60(g) required each laboratory performing tests related to the production of a PET drug to keep complete records of all tests performed to ensure compliance with established specifications and standards, including examinations and assays. The specific records required were set forth in proposed § 212.60(g)(1) through (g)(5). Proposed § 212.60(g)(1) required 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. Proposed § 212.60(g)(2) required 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. Proposed § 212.60(g)(3) required 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. Proposed § 212.60(g)(4) required a statement of the results of tests and how the results compare with established acceptance criteria. Proposed § 212.60(g)(5) required the initials or signature of the person performing the test and the date on which the test was performed.

(Comment 29) Several comments objected to the proposed requirements for test records, in particular the description of the sample received for testing. One comment stated that the required documentation needs streamlining because of limited time and human resources during production and quality control activities. The comment maintained that the proposed level of documentation is excessive in the presence of comprehensive and verified procedures.

Several comments maintained that the proposed requirements are excessive because the testing is conducted in the same room as, contiguous to, or in close proximity to the production area, often by the same personnel responsible for the production of the drug. One comment recommended that the guidance include a reduced requirement for when testing is performed contiguous with PET drug production.

One comment stated that the reference to the batch or lot number in proposed § 212.60(g)(1) is more than adequate. Two comments recommended revising § 212.60(g)(1) to state simply that samples received for testing must be suitably identified to avoid mix-ups.

Three comments maintained that the information that would be required under proposed § 212.60(g)(1) is already in the master formula and/or in individual batch records. One comment recommended that we clarify that existing documentation could satisfy the requirements for test records in § 212.60(g).

One comment recommended having separate test record requirements for: (1) Components, in-process materials, and PET drug products tested in a facility physically external to the manufacturing facility and (2) PET drug products tested internally. For the first group, the test record requirements in proposed § 212.60(g)(1) through (g)(5) would apply. The requirements for PET drug products tested internally would be the same, except that in lieu of a provision requiring a description of the sample received for testing, there would be a provision stating that ''[t]est records for PET drug products tested internally shall be inclusive to the batch record for that PET drug product.''

(Response) We agree with the comments that the proposed requirements for describing the sample received for testing should be changed to reflect the typical production and testing circumstances described by the comments. Therefore, we have revised § 212.60(g)(1) to require a ''suitable identification of the sample received for testing.'' Suitable identification of the sample means information that will provide complete traceability of the sample to the batch or lot from which the sample was taken. We agree with the comments that a PET drug producer might be able to meet this requirement by referring to information in the master production and control record or the batch production and control record. The revised § 212.60(g)(1) reflects that the information needed to identify a sample might vary depending on the circumstances under which production and testing are conducted. In particular, the revised provision obviates the need for separate provisions for: (1) Components, in-process materials, and PET drug products tested in a facility physically external to the manufacturing facility and (2) PET drug products tested internally.

H. Controls and Acceptance Criteria (Proposed § 212.70)

1. Specifications

Proposed § 212.70(a) would have required a PET drug producer to establish specifications for each batch of a PET drug product, including criteria for determining identity, strength, quality, purity, and, if appropriate, sterility and pyrogenicity.

(Comment 30) One comment stated that it seems more appropriate to set specifications for apyrogenicity rather than pyrogenicity.

(Response) An injectable PET drug product will have as part of its specifications a test and acceptance criteria for pyrogens. Therefore, we have revised § 212.70(a) to refer to ''pyrogens'' rather than ''pyrogenicity.''

In addition, on our own initiative, we have revised § 212.70(a) to state that a PET drug producer must establish specifications for ''each PET drug product'' rather than for ''each batch of a PET drug product.'' We intend the revision to make clear that the specifications are for each PET drug product and that these specifications may not differ from batch to batch of the product.

2. Conformance to Specifications

Proposed § 212.70(c) would have required a PET drug producer, before final release, to 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. The proposed provision would have further required that, 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.

(Comment 31) We did not receive any comment specifically referring to proposed § 212.70(c). However, one comment recommended adding a new paragraph (g) to § 212.70 to

accommodate testing of a PET drug product on something less than a per-batch basis. The comment stated that many tests are amenable to daily or skip testing. As an example, the comment referred to FDG F 18. The comment maintained that the bacterial endotoxin test for FDG F 18 always generates a nondetectable result because the alumina cartridge in the FDG production process removes all endotoxins. The comment also claimed that radiation levels for a bombarded target render the target and its contents sterilized by ionizing radiation, and repeated passage of commercial quantities of FDG F 18 through a production process renders the fluid pathway sterilized by ionizing radiation. According to the comment, the sterility assurance level achieved by exposure to ionizing radiation and passage of the active pharmaceutical ingredient through a sterilizing membrane filter renders a retrospective sterility test moot. Therefore, the comment recommended adding a provision stating as follows: ''You must conduct process verification and establish procedures for finished product testing on a daily basis rather than every batch of finished product.''

(Response) We do not agree with the comment that the bacterial endotoxin test for FDG F 18 always generates a nondetectable result; we are aware of at least one instance in which a batch of FDG F 18 was recalled due to endotoxin problems. However, we agree that finished-product testing is not the only method that can be used to demonstrate that a PET drug product conforms to its specifications. Other approaches may be appropriate for certain specifications. To reflect this, we have revised § 212.70(c) to require, before final release, ''an appropriate laboratory determination'' to ensure that each batch of a PET drug product conforms to specifications, except for sterility. For a PET drug product produced in sub-batches, before final release, ''an appropriate laboratory determination'' is required to ensure that each sub-batch conforms to specifications, except for sterility.

Examples of PET drug product specifications—the measurements of critical quality attributes that are indicative of the product's safety and effectiveness—include radiochemical identity and purity (including chiral purity), assay (including radioconcentration), specific activity, radioactive and non-radioactive impurities, and sterility. An appropriate laboratory determination to ensure that each batch (or, for a product produced in sub-batches, each sub-batch) of a PET drug product conforms to specifications under § 212.70(c) could involve the following:

- Finished-product testing of each batch;
- In-process testing of an attribute that is equivalent to finished-product testing of that attribute;
- Continuous process monitoring of attributes with statistical process controls;
- Some combination of these approaches.

Using finished-product testing alone would require testing each batch of a PET drug product for conformance to all specifications. In-process testing might involve use of an on-line test to determine whether an attribute meets an appropriate acceptance criterion, provided that the relevant attribute does not change during the production of the finished product. Under this scenario, the in-process testing of an attribute could be an adequate substitute for the finished-product testing for that attribute. Continuous process monitoring with statistical process controls involves comprehensive testing of attributes using on-line monitoring and corresponding adjustments to prevent an upward or downward drift in batch-to-batch measurements of an attribute. Depending on the particular PET drug product and specification, any of the suggested approaches might be appropriate for conducting an appropriate laboratory determination to ensure that each batch of the product conforms to the specification. The laboratory determination approach for each specification should be set forth in the product's marketing application.

Although § 212.70(c) addresses conformance to specifications, we recognize that there may be attributes of a PET drug product that, although not as significant as those included in the specifications, are nevertheless important in assessing the quality of the product. Examples of these noncritical attributes might include radionuclidic purity (when potentially contaminating radionuclides do not impact the safety or effectiveness of the drug product), as well as certain low-level nontoxic impurities and class three residual solvents. These noncritical attribute tests, referred to as periodic quality indicator tests (PQITs), are additional to tests conducted for conformance to drug product specifications. A PQIT is performed at predetermined intervals rather than on a batch-to-batch basis. A PET drug producer generally establishes and refines tests of noncritical attributes within its internal quality system. However, the sponsor of a PET drug product should seek approval of a PQIT for a noncritical attribute in the product's marketing application. FDA will review the frequency of PQIT testing during CGMP inspections.

3. Final Release Procedures

Proposed § 212.70(d) stated that a PET drug producer must establish and follow procedures to ensure that a PET drug product is not given final release until the following are done: (1) Appropriate laboratory testing under § 212.70(a) 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.

At our own initiative, we have revised § 212.70(d) to state that except as conditional final release is permitted in accordance with § 212.70(f), a PET drug producer must establish and follow procedures to ensure that a each batch of a PET drug product is not given final release until the steps in § 212.70(d)(1) through (d)(3) are done. This makes clear that compliance with the conditional final release procedures for a particular batch constitutes an exception to the requirement that each batch comply with final release procedures.

In addition, consistent with the change that we have made to proposed § 212.70(c), we have revised the first criterion in § 212.70(d) (i.e., § 212.70(d)(1)) to require completion of an ''appropriate laboratory determination under paragraph (c)'' rather than appropriate laboratory testing under § 212.70(a).

4. Sterility Testing

Proposed § 212.70(e) stated that sterility testing need not be completed before final release but must be started within 30 hours after completion of production; the 30 hours might be exceeded because of a weekend or holiday. Proposed § 212.70(e) further stated that if the sample for sterility testing is held longer than indicated, the PET drug producer 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. Proposed § 212.70(e) also stated that 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.

On our own initiative, we have revised the second sentence of § 212.70(e) to clarify that if the sample for sterility testing is held longer than 30 hours (rather than as ''indicated''), the PET drug producer must take the actions specified in that sentence. Also on our own initiative, we have revised § 212.70(e) to state that ''[t]ested samples must be from individual batches and not pooled,'' rather than stating that ''[p]roduct samples must be tested individually and must not be pooled.'' This clarifies that a sample from each batch of a PET drug product must be tested for sterility.

(Comment 32) Several comments objected to the proposed requirement to notify receiving facilities immediately if a PET drug product fails the sterility test. Several comments stated that although detection of a growth in an inoculated media should prompt an investigation, it does not necessarily equate to sterility failure. Two comments stated that an investigation of a test failure should lead to an informed determination as to whether the batch was not sterile or a technical error caused a false positive result, and that notification is justified only if nonsterility is confirmed. Two comments stated that the results of an investigation into a sterility test failure might not be known for 2 to 4 weeks. One comment stated that the notification required by proposed § 212.70(e) would occur several days after administration of the drug product and critical data, such as species identification, would not be available. Three comments stated that immediate, unqualified notification would be alarming and unproductive.

To address concerns about proposed § 212.70(e), four comments recommended that this provision require that receiving facilities be notified if an investigation into a nonconforming sterility test concludes that a drug product was non-sterile. One comment, stating that it was questionable what benefit would be served by notification at this point and what advice would be appropriate and meaningful, asked that we reconsider this requirement or include recommendations in the PET CGMP guidance on what to tell the receiving facility.

(Response) We understand that initial results from conventional sterility tests are not definitive, and we appreciate that it takes some time to investigate a failed test. However, we believe that it is important to convey to the clinician the potential risks to a patient when a PET drug product initially fails to meet a criterion for sterility. We have revised § 212.70(e) to clarify that, if a product fails to meet a criterion for sterility, the PET drug producer must immediately notify all facilities that received the product of the test results and provide any appropriate recommendations. Consistent with the need to keep receiving facilities adequately informed, we have added to § 212.70(e) a requirement that, upon completion of an investigation into a failure to meet a criterion for sterility, the PET drug producer must notify all facilities that received the product of the findings from the investigation.

(Comment 33) Two comments, noting that the draft guidance states that sterile PET drugs can be distributed after initiation of an endotoxin test but before obtaining test results (provided the results are determined to meet acceptance criteria before the drug product is administered to humans), requested that this procedure be included in the regulations.

(Response) We do not believe that it necessary to establish a regulation as requested. Under § 212.70(c), endotoxin testing must be completed before final release of a PET drug product. The guidance simply clarifies that, because of the short half-lives of many PET drugs, a product can be ''distributed under control after a pharmacopeial bacterial endotoxin test is initiated. However, the endotoxin results should meet the acceptance criteria before administering the product to humans.'' Distribution under control does not constitute final release of the product; final release can only occur after the completion of the laboratory determination to ensure conformance to specifications (except for sterility). Distribution control procedures, including any agreements between the PET drug producer and receiving facilities, should be specified in a standard operating procedures (SOPs) document.

5. Conditional Final Release

Proposed § 212.70(f) set forth the conditions under which conditional final release of a PET drug product would be permitted.

a. *Conditions for release (proposed § 212.70(f)(1)).* Proposed § 212.70(f)(1) stated that if the PET drug producer cannot complete one of the required finished product tests for a PET drug product because of a breakdown of analytical equipment, the producer may approve the conditional final release of the product if it meets the following conditions (listed in proposed § 212.70(f)(1)(i) through (f)(1)(vii)):

- The PET drug producer has 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;
- The PET drug producer determines that all other acceptance criteria are met;
- The PET drug producer immediately notifies the receiving facility of the incomplete testing;
- The PET drug producer retains a reserve sample of the conditionally released batch of drug product;
- The PET drug producer completes the omitted test using the reserve sample after the analytical equipment is repaired and documents that reasonable efforts have been made to ensure that the problem does not recur;
- If an out-of-specification result is obtained when the reserve sample is tested, the PET drug producer immediately notifies the receiving facility; and
- The PET drug producer documents 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.

i. *Circumstances justifying conditional final release (proposed § 212.70(f)(1)).* At our own initiative, we have revised § 212.70(f)(1) to clarify that conditional final release may be appropriate when a PET drug producer cannot complete one of the required finished-product tests for a particular batch of a PET drug product because of a malfunction involving analytical equipment (proposed § 212.70(f)(1)(i) and (f)(i)(iv), but not (f)(1), had referred to conditionally released batches).

(Comment 34) Three comments objected to the proposed criteria for conditional final release because they believe the criteria are partially inconsistent with the Tests and Assays section of the USP's General Notices. Two comments stated that according to the Tests and Assays section, process validation and in-process controls may provide greater assurance that a drug product conforms to release specifications than conducting each test on every final product batch. One comment stated that proposed § 212.70(f)(1) inaccurately implies that every pharmacopeial test is required before release to assure quality. Two comments recommended that § 212.70(f)(1) be revised to state that if a PET drug producer cannot complete one of the finished-product release tests on a timely basis because of an analytical equipment breakdown,

inconclusive result, or invalid condition, the producer may approve conditional release of a batch if there is historical evidence to substantiate that the product will likely meet the established specifications. One comment stated that such a release test should be one that is stipulated in an approved application. One comment also stated that the producer should be required to implement written procedures that: (1) Determine which finished-product tests are applicable for conditional release, (2) specify the steps required to correct the cause of the invalid condition or equipment failure in a timely fashion, and (3) document all conditional release activities.

(Response) We agree with the comments that the USP does not require the completion of every pharmacopeial test on each product batch prior to release of the batch. Instead, the USP states that every article, when tested, should conform to the monograph. However, § 212.70(c) requires that the PET drug producer conduct an appropriate laboratory determination to ensure that each batch of a PET drug product conforms to specifications, except for sterility, before final release of the product. Although many of the critical laboratory tests must be completed before final release, we agree that it is appropriate to broaden the circumstances under which a PET drug producer may approve the conditional final release of a product. Therefore, we have revised § 212.70(f)(1) to allow conditional final release if the PET drug producer cannot complete one of the required finished-product tests for a PET drug product because of a malfunction involving analytical equipment, rather than solely a complete breakdown of such equipment. For example, gas chromatography equipment might be operating but producing inaccurate results because of some malfunction. Conditional release due to an equipment malfunction might be appropriate when test results are atypical but other process indicators show that release of raw materials and production and purification process events have occurred as expected. For example, a PET drug producer might observe a baseline drift in a high pressure liquid chromatography (HPLC) analysis for a product, but if the peak shape is similar to what is normally seen and the production and purification events have progressed as expected, it might be reasonable to conclude that there is an equipment malfunction, rather than that the product is contaminated. In such a case, conditional final release of the product would be appropriate. For these reasons, the revised § 212.70(f)(1) more accurately reflects the range of circumstances under which conditional final release might be appropriate.

However, we do not agree with the proposal to allow conditional final release when there is an ''inconclusive result'' or an ''invalid condition,'' because those terms are so broad and vague that they might permit conditional final release when there is too much uncertainty about the safety and quality of the drug product. For similar reasons, we do not believe that it is appropriate to allow each PET drug producer to determine which finished-product tests may be omitted under conditional final release. We do not believe it is necessary to require that the approved application specify all the tests that need not be completed for conditional final release, as long as conditional final release is limited to circumstances in which there is a malfunction involving analytical equipment.

In addition, we do not believe it is necessary for § 212.70(f) to specifically require that PET drug producers have written procedures for conditional final release, as requested by one comment, because the provision itself essentially states those procedures. Consistent with the comment, however, § 212.70(f)(vi) requires documentation of all actions regarding conditional final release, including corrective actions to prevent recurrence of a particular malfunction involving analytical equipment.

We have revised the definition of ''conditional final release'' in § 212.1 to correspond to this change by replacing ''breakdown of analytical equipment'' with ''malfunction involving analytical equipment.''

ii. *Notification of incomplete testing (proposed § 212.70(f)(1)(iii)).* (Comment 35) Several comments recommended deletion of the requirement in proposed § 212.70(f)(1)(iii) to immediately notify the receiving facility of incomplete testing. Four comments stated that the personnel at the receiving facility are not knowledgeable of the conditional release allowance and lack the expertise to interpret the meaning of such a release in the context of patient safety and product efficacy. The comments stated that notifying the receiving facility in these circumstances would cause uncertainty and undue apprehension, which would not serve the best interest of patients. Three comments stated that other provisions in proposed § 212.70(f)(1) provide adequate protection to patients; for example, proposed § 212.70(f)(1)(vi) provides for immediate notification of the receiving facility if subsequent testing reveals an out-of-specification result.

(Response) We agree that immediate notification of the receiving facility of incomplete product testing would not provide sufficient information to make the requirement worthwhile. Therefore, we have deleted this condition from § 212.70(f)(1).

iii. *Completion of omitted test and efforts to ensure that the problem does not recur (proposed § 212.70(f)(1)(v)).* At our own initiative, we have revised § 212.70(f)(1)(v) (now § 212.70(f)(1)(iv)) to require that a PET drug producer promptly correct the malfunction of analytical equipment, complete the omitted test using the reserve sample after the malfunction is corrected (rather than after the analytical equipment is repaired, consistent with the change to § 212.70(f)(1)), and document that reasonable efforts have been made to prevent recurrence of the malfunction. In connection with this change, we have added § 212.70(f)(3), which states that a PET drug producer may not release another batch of PET drug product following the conditional release of a batch of the product until the producer has corrected the problem concerning the malfunction of analytical equipment and completed the omitted finished-product test. We believe that these changes are appropriate to provide assurance that patients receive safe and effective PET drug products. We conclude that these changes will not impose a significant additional burden on PET drug producers because we believe that in most of the rare instances in which a malfunction of analytical equipment occurs, PET drug producers seek to quickly correct the malfunction and typically do not release additional batches of the drug until the problem is corrected. In addition, many medical facilities that produce and administer PET drugs may be able to obtain PET drugs for their patients from other PET drug producers while they are correcting an equipment malfunction in accordance with § 212.70(f)(1)(iv). For these reasons, we have revised § 212.70(f)(1)(iv) and added § 212.70(f)(3) as stated.

(Comment 36) Regarding completion of the omitted test under proposed § 212.70(f)(1)(v), two comments stated that, depending on when analytical equipment is repaired, the PET drug producer might not be able to obtain meaningful data for testing (e.g., radionuclidic identity or purity) because the radioactivity of the radionuclide might be decayed to background level. Therefore, the comments recommended revising the provision to state that the

PET drug producer should complete the omitted test, if possible, using the reserve sample after the analytical equipment is repaired.

(Response) Although we agree that some critical tests cannot be performed at a later time (i.e., after correction of an analytical equipment malfunction) because of the short half-life of a product, we do not believe that it is appropriate to revise § 212.70(f)(1)(v) to require completion of the omitted test only ''if possible'' after the malfunction is corrected. With respect to radionuclidic identity, a dose calibrator is required for testing. If the dose calibrator is not functioning properly, we believe that the dose of the product cannot be accurately measured. As for radionuclidic purity, we believe that it is possible to conduct the test on a decayed sample of the product. We recommend that PET drug producers develop alternate tests for specifications for which they conclude it is not possible to conduct a particular test after an analytical equipment malfunction has been corrected. For example, if a dose calibrator malfunctioned and the activity of a product could not be assayed, a sample of known dilution could be counted using other equipment, and the activity concentration could be determined by correcting for counting efficiency and dilution.

(Comment 37) Three comments stated that it will never be possible to ''ensure'' that a breakdown of analytical equipment will not recur, as expected in proposed § 212.70(f)(1)(v). Two comments recommended substituting ''prevent recurrence of the problem'' for ''ensure that the problem does not recur.'' One comment recommended substituting ''document the repair and corrective and preventive actions'' for ''document that reasonable efforts have been made to ensure that the problem does not recur.''

(Response) We agree that it is more appropriate to require a PET drug producer to document that reasonable efforts have been made to prevent recurrence of the malfunction involving analytical equipment. Therefore, we have revised § 212.70(f)(1)(v) (now § 212.70(f)(1)(iv)) accordingly.

iv. *Notification of an out-of-specification result (proposed § 212.70(f)(1)(vi)).* (Comment 38) One comment recommended deletion of the requirement for the PET drug producer to immediately notify the receiving facility if the producer obtains an out-of-specification result when testing the reserve sample. The comment stated that personnel at the receiving facility would not have sufficient understanding of such regulatory action or expertise to decide whether to administer the drug. The comment stated that such notification would create confusion and undue concern at the receiving facility.

(Response) We do not agree. Notifying receiving facilities of out-of-specification results so that personnel can take appropriate action, usually to prevent administration of the drug, is consistent with the intent of CGMP to ensure that patients receive appropriate PET drugs. This differs from the situation involving notification of incomplete product testing under proposed § 212.70(f)(1)(iii), in which it is still possible that the batch may actually conform to specifications and therefore be appropriate for administration to patients.

v. *Documentation of actions regarding conditional final release (proposed § 212.70(f)(1)(vii)).* Consistent with the changes to § 212.70(f)(1) and (f)(1)(iv), we revised § 212.70(f)(1)(vii) (now § 212.70(f)(1)(vi)) to require documentation of all actions regarding the conditional final release of the drug product to prevent recurrence of the malfunction involving analytical equipment (rather than to ensure that the equipment breakdown does not recur).

b. *Inability to perform radiochemical identity/purity test (proposed § 212.70(f)(2)).* Proposed § 212.70(f)(2) stated that even if the criteria in § 212.70(f)(1) were met, a PET drug producer could not approve the conditional final release of a PET drug product if the breakdown in analytical equipment prevented the performance of a radiochemical identity/purity test.

(Comment 39) One comment stated that § 212.70(f)(2) should also disallow conditional final release if the breakdown in analytical equipment prevents the determination of the specific activity of a PET drug product with mass-dependent target localization and/or potential to elicit a physiological effect, where the specific activity limit is quantitatively expressed.

(Response) We agree. Therefore, we have revised § 212.70(f)(2) to state that a PET drug producer may not approve the conditional final release of a product if the malfunction involving analytical equipment prevents the performance of a radiochemical identity/purity test or prevents the determination of the product's specific activity.

I. Actions To Be Taken If Product Does Not Conform to Specifications (Proposed § 212.71)

Proposed § 212.71 addressed the actions that a PET drug producer must take if a batch of a PET drug product does not conform to specifications. Proposed § 212.71(d) stated that, if appropriate, a PET drug producer may reprocess a batch of a PET drug product that does not conform to specifications. The proposed provision further stated that if material that does not meet acceptance criteria is reprocessed, the PET drug 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.

(Comment 40) One comment asked whether such reprocessing was required to be specified in the approved NDA for the PET drug product or whether it could be done according to an internal process for the establishment of production and process controls.

(Response) Reprocessing a batch of PET drug product that did not conform to specifications is only appropriate if the reprocessing is included in the approved NDA or ANDA for the product. To clarify this provision, we have revised the second sentence of § 212.71(d) to state that if material that does not meet acceptance criteria is reprocessed, the PET drug producer must follow ''procedures stated in the product's approved application'' (which could be either an NDA or ANDA).

J. Complaint Handling (Proposed § 212.100)

1. Written Complaint Procedures

Proposed § 212.100(a) stated that a PET drug producer must develop and follow written procedures for the receipt and handling of all complaints concerning a PET drug product.

(Comment 41) Three comments objected to the scope of proposed § 212.100(a). The comments stated that it would be inappropriate for § 212.100(a) to include complaints involving such matters as pricing issues, ordering errors, and shipping delays. One comment stated that the provision should be limited to complaints concerning the quality or purity of, or possible adverse reactions to, a PET drug product. In addition to recommending inclusion of complaints about adverse reactions, one comment suggested including complaints about the quality or labeling of a PET drug product and another comment recommended including complaints about the quality or efficacy of a PET drug product.

(Response) We agree with the comments that PET drug producers should not be required to have written procedures regarding all conceivable

complaints about a PET drug product. Therefore, we have revised § 212.100(a) to state that a PET drug producer must develop and follow written procedures for the receipt and handling of all complaints concerning the quality or purity of, or possible adverse reactions to, a PET drug product.

2. Returned Products

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

(Comment 42) One comment asked us to clarify whether proposed § 212.100(d) was intended to allow the reprocessing of returns that are not the result of complaints.

(Response) We can conceive of no circumstances under which a returned PET drug product could be reusable. Therefore, we have revised § 212.100(d) to state that a PET drug product that is returned because of a complaint or for any other reason may not be reprocessed and must be destroyed in accordance with applicable Federal and State law.

K. Records (Proposed § 212.110)

Proposed § 212.110(c) stated that a PET drug producer must maintain all records and documentation referenced in other parts of the regulation for a period of at least 1 year from the date of final release, including conditional final release, of a PET drug product. On our own initiative, we revised this provision to clarify that it requires the maintenance of all records and documentation referenced in part 212.

IV. Analysis of Economic Impacts

We have examined the potential economic impact of this final 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 net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). We believe that this final rule is not an economically significant action under the Executive order.

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 this rule may have a significant effect on a substantial number of small entities. A regulatory flexibility analysis explaining this finding is presented below.

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 $133 million, using the most current (2008) Implicit Price Deflator for the Gross Domestic Product. We do not expect this final rule to result in any 1-year expenditure that would meet or exceed this amount.

A. Regulatory Benefits

Comments on the proposed rule did not focus specifically on our description of the benefits of the proposed CGMP regulations for PET drugs. Further, none of the changes made to the final rule cause us to re-examine these benefits. We therefore present the same qualitative description of the benefits of the final rule.

The Modernization Act requires us to establish appropriate good manufacturing practices for PET drugs. Without minimum manufacturing standards, unintentionally inferior PET drugs may be produced for human use. The short half-life characteristic of PET drugs 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 drugs are marketed without FDA approval, and we have not received any 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 for the proposed rule, we were unable to estimate how much this rule might reduce the risk of adverse events associated with PET drugs and consequently improve public health. As stated previously, comments on the proposed rule did not offer any data concerning the expected level of risk reduction due to compliance with the CGMP requirements. Because the final rule is not substantially different from the proposed rule, we maintain that the final rule will reduce, by an unquantifiable amount, the risk of adverse health events associated with PET drugs.

This rule creates minimum manufacturing standards to ensure the safety, identity, strength, quality, and purity of PET drugs. Building quality into the production process permits early detection and correction of problems and promotes continuous improvement. Activities such as developing specifications may result in increased reliability and uniformity of PET drugs to patients. Ultimately, this rule is expected to result in a reduction in adverse reactions to PET drugs and an improvement in overall public health.

B. Regulatory Costs

Public comments did not specifically address the methodology of the analysis of impacts section that was published in the proposed rule. As such, we retain it for the analysis of the final rule. For the proposed rule, we determined that many PET drug producers had already adopted some form of good manufacturing practices or SOPs. The Modernization Act required 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 expected average compliance costs associated with the proposal to be small.

We proposed that the CGMP rule would 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. We believed that most of the large corporate PET drug producers and hospital PET drug producers associated with these corporate entities already complied to a great degree with the proposed CGMP rule. Based on our consultations with industry (including PET drug producers and professional associations) through direct contact as well as public comments at public meetings and previously published preliminary proposed rules, we made a general assessment of the current operational status of PET drug producers for the proposed rule.

We estimated that the proposed rule would affect 51 producers of PET drugs, operating 101 establishments. Fifteen of these producers owned or operated 65

commercial establishments (16 of which are associated with academic hospitals). Of these 15 producers, 11 were regional or local unaffiliated producers that had begun to produce PET drug products in recent years. The other four commercial producers were corporations, each of which had multiple establishments. In total, these 4 corporate producers operated 48 establishments. The remaining 36 producers were 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 or 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

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

The following sections contain the general requirements of the final 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 PET drugs. 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 drug products.
- Section 212.100: Establish procedures for the receipt and handling of complaints regarding a PET drug product.

1. Impact of Changes to the Proposed Rule

Among the revisions we made to the proposed rule are several changes that could affect the compliance costs of the rule. We revised § 212.50(c)(6) to require that the time of production of PET drugs be recorded only for critical production steps. This is expected to slightly reduce the burden of the final rule on PET drug producers. We revised § 212.60(g)(1) to require only that any sample of a PET drug product received by a laboratory for testing be suitably identified, rather than requiring a description of the sample, including information that may already be included in the master production and control record. Under this change, a reference to the information in the master production and control record would simplify the identification procedure by eliminating the need for an employee to re-enter identical data, which would slightly reduce labor costs for PET drug producers.

We revised § 212.70(c) to allow for more flexibility in the determination of batch specificity conformity by not requiring finished-product testing in all circumstances. This change represents another slight reduction in compliance costs. We revised § 212.70(e) to require that, upon completion of an investigation into the failure to meet a criterion for sterility, all facilities that received the PET drug product be notified of the findings of the investigation. Because providing this notification appears to be the current practice among PET drug producers, no additional compliance costs are expected to result from this change. We slightly reduced potential compliance costs under § 212.70(f)(1) by broadening the circumstances under which conditional final release is permitted to include when there is a malfunction involving analytical equipment (instead of only when a complete breakdown occurs). Our deletion from § 212.70(f)(1) of the requirement that the PET drug producer immediately notify the receiving facility if incomplete testing occurs also slightly reduces compliance costs. Finally, we revised § 212.70(f)(2) to prohibit approval of conditional final release of a PET drug product if an equipment malfunction prevents the determination of the product's specific activity. Although this revision specifies another circumstance under which conditional final release of a PET drug product is not permissible (in addition to when a malfunction prevents the performance of a radiochemical identity/purity test), the change is consistent with current practice and therefore creates no additional compliance burden.

For the annual costs of the proposed rule, we developed estimates based on input from agency resources that a quality control manager of a PET drug production facility would put forth from 3 to 7.5 additional labor hours weekly to comply with the CGMP regulations. The changes to the final rule outlined

above would likely result in a slightly smaller burden due to reduced labor hours that may total only a few minutes weekly. Since the size of the reduction in burden is so small and likely within any range of uncertainty inherent in the estimates made for the proposal, we have not changed the estimated labor hour increases in the analysis of this final rule.

We expect some variation in the exact SOPs that PET drug producers will need to create or revise to comply with the rule. We expect that the various types of producers already comply with aspects of the rule to different extents. The hospital PET drug producers and the independent regional commercial producers will likely require more time and effort to comply than will 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.

2. 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 will be included in the efforts of a designated individual or individuals who will be primarily responsible for bringing each PET drug production establishment into compliance. In this case, we 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 titled ''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 incoming component tracking and testing records. PET drug producers will 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.

For the final rule, we have increased all employment costs by about 21.7 percent to account for the employment cost increase from 2001 (the year for which we estimated salary and labor costs) to 2007.[2] We estimate that all hospital and regional commercial producers will need from 3 to 5 months to write and establish the SOPs, even with the guidance provided. We assume that the employee responsible for writing the SOPs will be in a management position, either in quality assurance or elsewhere, with a salary of up to $121,700 per year; we include an additional 35 percent for employee benefits and other costs for an annual cost per employee of $164,300 ($121,700 x 1.35). The cost of an average 4-month effort will therefore amount to $54,800 for each hospital and regional commercial PET drug producer.[3]

Although most corporate PET drug producers are said to have a complete set of SOPs, we assume each will expend some time to verify its compliance with the rule and make minor adjustments to their SOPs. We estimate that it will take, on average, 1 month for an individual to verify compliance with the rule and make any needed adjustments to the SOPs. This will result in a cost of approximately $13,700 per corporate PET drug producer, again using an estimated salary and benefits of $164,300 per year. The smaller burden for corporate PET drug producers compared with hospitals and regional producers is due to the current high compliance rates expected at the corporate establishments.[4] We also assume that corporate producers with multiple manufacturing sites will amend a single set of SOPs to cover all of their production sites. Since there are currently four corporate producers of PET drugs, the cost of the SOP revisions is estimated at $54,800 (4 times $13,700).

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 will be more likely at the hospital and regional commercial PET drug producers, we do not expect the total cost of this compliance effort to vary considerably.

Producers also are 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 will be necessary at most establishments, we projected that one person at each establishment could need up to 1 week of additional training. The cost of this additional training amounts to about $319,000 (101 establishments times 1 week at $164,300 per year).

The total cost for initial compliance associated with writing the SOPs and creating document forms amounts to approximately $2.95 million. The 47 hospital and regional commercial producers will incur a total of about $2.75 million (47 producers times $54,800 plus 53 establishments times $3,200). The 4 corporate producers will incur a total of about $207,000 (4 producers times $13,700 plus 48 establishments times $3,200). Annualizing the total one-time cost over 5 years at a 7 percent discount rate results in annualized costs of about $719,000.

Once procedures are established and documents are in place to record PET drug production and events associated with routine production of PET drugs, we 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 will have to be expanded to include any provisions with which the company is 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 will 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 rule will require, at most, one to two additional hours per day for an individual at each hospital or regional commercial producer. Using the midpoint of this range results in 2.25 additional months of labor each year. Using the same estimated annual salary ($121,700 plus benefits), 2.25 months of labor equates to about $30,800 in annual costs to each PET drug production establishment, or about $1.63 million for all 53 hospital and regional commercial producer establishments.

Our assessment of corporate PET drug producers is that they already comply substantially with the rule. For these

[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/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm*).

[2] U.S. Department of Labor, Bureau of Labor Statistics, private industry, total compensation.

[3] 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 or hospital producers, we assume they would pay a salary similar to those of corporate producers.

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

producers, we project that one production individual will expend an additional 1 month of effort over the course of each year (about 3 hours per week) to comply with the rule. This month will result in each corporate PET drug producer incurring about $13,700 in additional annual costs, totaling $657,000 for the 48 corporate PET drug production establishments. Some producers will probably opt to use an outside consultant to manage the implementation of the new regulations in the first year. Although we do not know how many producers will hire a consultant, we do 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 for hospitals and regional producers as well as corporate producers are estimated at $2.29 million ($1.63 million plus $657,000).

Producers also are expected to provide some additional training in future years on SOPs that were amended to comply with this CGMP rule. We expect that this training (review for current employees as well as new employees) will be incorporated into current training programs and therefore be less burdensome than the initial training to implement the rule. Nevertheless, we included the cost for annual training for one person per establishment for one-half week. The cost of this additional training amounts to about $160,000 annually (101 establishments times one-half week at $164,300 per year).

Total annual costs associated with daily implementation and training amount to $2.45 million. The 53 hospital and regional commercial establishments will incur a total of about $1.72 million (53 establishments times ($20,800 plus $1,600)). The average cost per facility for these provisions is $32,400. The 48 corporate production establishments will incur a total of about $734,000 (48 establishments times ($13,700 plus $1,600)). The average cost per facility for these provisions is $15,300.

3. Equipment Costs

Based on numerous site visits to PET drug production facilities by FDA personnel, we conclude that the current laboratory facilities and equipment comply with the requirements of the final rule. Therefore, additional costs for laboratory space or equipment will not be incurred in complying with the rule. 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 will not be required.

4. Process Verification Costs

In response to public comments on the preliminary draft proposed rule, we modified the process verification requirements. Not all PET drug product batches that undergo full finished-product testing to ensure that the product meets specifications will be required to verify the production process. Since we believe that all PET drugs that will receive NDA approval in the next few years will undergo finished-product testing, this requirement will not impose any additional burden. In later years, however, some PET drugs products with NDA approval may submit only the initial sub-batch to finished-product testing before release. In such cases, producers will have to document their process verification procedures. Since we do not know how many, if any, PET drugs such as this will 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.

5. Total Costs

Total one-time costs are estimated at about $2.95 million (annualized at $720,000 over 5 years), and annual costs at about $2.45 million (see table 2 of this document).

TABLE 2.—CGMP COSTS BY REQUIREMENT

Rule Requirement	No. of Establishments	Labor (Months)	Wage (Yr. Sal.)[1]	Cost[2]
One-Time Costs				
Establishment/Write SOPs				
Academic PET Producers	47	3	$164,300	$2,574,000
Commercial PET Producers	4	1	$164,300	$55,000
Training on SOPs				
Academic PET Producers	53	.23	$164,300	$168,000
Commercial PET Producers	48	.23	$164,300	$152,000
Total One-Time Costs				$2,949,000
Annual Costs				
Rule Requirement				
Daily Implementation, Audits, Updates				
Academic PET Producers	53	2.25	$164,300	$1,633,000
Commercial PET Producers	48	1.0	$164,300	$657,000
Training				

TABLE 2.—CGMP COSTS BY REQUIREMENT—Continued

Rule Requirement	No. of Establishments	Labor (Months)	Wage (Yr. Sal.)[1]	Cost[2]
Academic PET Producers	53	.11	$164,300	$84,000
Commercial PET Producers	48	.11	$164,300	$76,000
Total Annual Costs				$2,450,000

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

As shown in table 3 of this document, the 53 hospital and regional commercial PET drug production establishments will incur about $2.74 million in one-time costs and $1.72 million in annual costs. The annualized (annualized one-time costs plus annual costs) cost per facility is estimated at about $43,600. The 48 corporate PET drug production facilities will incur about $207,000 and $733,000 in one-time and annual costs, respectively. Total annualized (annualized one-time costs plus annual costs) costs per corporate establishment are estimated at about $16,300. Total annualized costs for all producers are estimated at $3,170,000.

TABLE 3.—CGMP COSTS BY TYPE OF ESTABLISHMENT

	One-Time Cost	Annual Cost
Hospital and Regional Commercial Establishments (53)	$2,740,000	$1,720,000
Corporate Establishments (48)	$207,000	$733,000
Total Cost[1]	$2,947,000	$2,453,000
Total Annualized Cost[2]		$3,170,000

[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.

For the proposed rule, we estimated, with some uncertainty, that 101 PET drug producers were in operation. While preparing the impacts analysis of the final rule, we requested information from an association of radiopharmaceutical manufacturers about the number of PET drug producers. The association responded with a count showing an estimated 135 to 145 sites operating cyclotrons that are capable of producing FDG F 18.[5] We are not certain that each of these 135 to 145 cyclotrons currently produces PET drugs, nor do the data identify the actual sites. However, we use the midpoint of this range, or 140 cyclotron sites, as the upper bound of the range of possible PET drug production sites. The association's data are not as detailed as the data we presented in the proposed rule, as the former do not show the distribution of production facilities among the different establishment types. We will, therefore, retain the relative distribution of production facilities we presented for the proposed rule and increase total industry costs by the relative increase in possible PET drug production sites, or 38.6 percent ((140 sites - 101sites) / 101 sites). If these additional 39 sites produce PET drugs, the total annualized costs would be as high as $4.40 million. Although our estimates of total industry costs would increase due to this adjustment (which we anticipated to some extent in the analysis of the proposed rule by projecting an annual 5-percent increase in the number of facilities), compliance costs per PET drug manufacturing facility will not increase with the larger estimate of total facilities.

We received one comment on our estimate of total costs. The comment expressed concern that subjecting hospitals and research institutions to the same inspection regime as large commercial producers would be unduly onerous, requiring those institutions to shift limited resources away from health care delivery and research to satisfy regulatory obligations that the comment believes are not warranted by clinical or safety considerations. A footnote to the comment stated that the proposed rule's compliance costs (e.g., $2.42 million one-time costs and $2 million in annual costs per hospital or corporate facility) were of particular concern.

We note that the $2.95 million in revised one-time costs and the approximately $2.45 million in revised annual costs represent totals for all PET drug establishments, not individual hospitals or corporate facilities. In addition, the cost figures reflect all costs associated with compliance with PET CGMP requirements, not simply costs related to FDA inspections, which is the focus of the comment's concern. Finally, we have addressed the comment's concern regarding inspections in our response to comment 6 in section III.A of this document.

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 drugs, 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 drugs is expected to continue to increase, we projected compliance costs over the next 10 years for the proposed rule. We did not receive comment on our projection and retain it (with adjustments for

[5] Correspondence to FDA from Council on Radionuclides and Radiopharmaceuticals, Inc., dated October 3, 2006.

employment cost inflation) for the final rule. 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 will be partially met by increasing production runs and batch sizes at existing establishments rather than proportional increases in the number of PET drug production establishments. We have therefore projected average annual PET drug production establishment increases will range from 3 to 7 percent. Assuming this growth occurs evenly across producer types, this growth rate implies an increase in annualized costs from $3.17 million in year one to $4.15 to $5.84 million in year ten. The PET drug risk reduction resulting from this rule will also apply to the additional volume of PET drug dosages implied by the 3- to 7-percent annual growth rate in PET drug establishments.

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 rule, in accordance with the Modernization Act, will help ensure the safety, identity, strength, quality, and purity of PET drugs by establishing CGMP requirements. The objective of the rule 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 drugs.

2. Definition of Small Entities

A regulatory flexibility analysis (RFA) is required to estimate the number of small entities to which the rule applies. Since we did not receive any comments on the proposed rule that addressed the analysis of impacts on small entities, we retain our analysis for the final rule, with revisions for inflation. This rule affects producers of PET drugs, including certain hospitals, clinics, colleges and universities, and producers of in vivo diagnostic substances. According to the Small Business Administration (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. To estimate the number of U.S. establishments producing PET drugs, we combined a list of PET centers with cyclotrons from the Academy of Molecular Imaging (AMI) with a list of PET manufacturing facilities from the Society of Nuclear Imaging in Drug Development, which has since merged with the AMI, and added additional facilities that we identified. We have identified 101 establishments operated by 51 PET drug producers. In over one-third of the cases, the PET drug is produced by a hospital. In other instances, a corporate producer manages production under contract at one or more hospitals with cyclotrons. PET drugs 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;
- Investor-owned (for-profit).[6]

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.[7] 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 $57.7 million using the Consumer Price Index (CPI) for medical care from 1997 to 2007. Considering that hospitals producing PET drugs probably are 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 are therefore not considered small entities.[8] 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 drugs 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 drugs it produces or the share of the market it holds.

3. Impact on Small Entities

The reporting, recordkeeping, and other compliance requirements on small entities 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 PET drug producer may incur one-time and annual costs of approximately $57,900 and $32,400, respectively, per production facility. The hospital and regional commercial producers will incur these higher per-facility costs because these establishments are expected to have higher noncompliance rates 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 $111 million ($70.8 million inflated by the CPI for medical care from 1997 to 2007) average annual gross revenue per nonprofit hospital. In addition, most of the hospitals that are affected by this rule are affiliated with large universities whose total revenues are expected to be much higher than the $111 million figure cited. The estimated compliance cost represents an even

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

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

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

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 is expected to incur annual costs of approximately $70,100 and one-time costs of about $16,800. The 11 regional commercial producers are expected to incur one-time and annual costs of approximately $57,900 per producer and $32,400 per production facility. We lack sufficient data to estimate the expected compliance costs as a percentage of revenues for the regional commercial producers. Although no comments on the proposed rule directly addressed our estimates of the expected impact of compliance costs on small facilities, it is possible that this final rule will have a significant effect on these small entities.

4. Other Federal Rules

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

5. Analysis of Alternatives

Several alternative provisions were considered in addition to those of the proposed rule. These included using traditional CGMPs, requiring specific identity testing of PET drug components, requiring verification of certificates of analyses of PET drug components, validating production and process controls, and requiring audit trail capabilities for all computer-operated systems. These alternative provisions were not included in the proposed rule because they were determined to be unnecessary, unduly burdensome, or both.

(Comment 43) We received one comment on electronic audit trail capabilities. The comment stated that, as we estimated, there is very little if any software of this nature in use by PET drug producers. The comment stated that many items of production equipment are incapable of the necessary software upgrades due to age and existing operating systems. The comment maintained that requiring the use of electronic audit trail software would be unduly burdensome for the PET community, and it recommended that we not require an electronic audit trail as part of PET CGMP provisions.

(Response) We agree that the additional level of quality assurance that might be provided through the use of electronic audit trail capability does not warrant the additional costs that would be imposed to implement this capability. Therefore, the CGMP requirements for PET drugs do not include electronic audit trail requirements.

We did not receive any public comments on the proposed rule concerning the analyses of the other alternative provisions of the proposed PET CGMP rule.

V. 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.

VI. Paperwork Reduction Act of 1995

This final rule contains information collection requirements that are subject to review by the Office of Management and Budget (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.

Title: Current Good Manufacturing Practice for Positron Emission Tomography Drugs

Description: In accordance with the Modernization Act, the final rule establishes CGMP requirements for PET drugs. The 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 estimated annual recordkeeping and third-party disclosure burden 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 CGMP regulations are intended to ensure that approved PET drugs meet the requirements of the act as to safety, identity, strength, quality, and purity. The regulations address the following matters: Personnel and resources; quality assurance; 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 CGMP regulations establish several recordkeeping requirements for the production of PET drugs. In making our estimates of the time spent in complying with these 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 drugs.

Burden Estimate: Table 4 of this document provides an estimate of the annual recordkeeping burdens associated with the final rule. Table 5 of this document provides an estimate of the annual third-party disclosure burdens associated with the final rule. 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, resulting in an estimated 173 total PET drugs. 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 will be required.

A. Investigational and Research PET Drugs

Section 212.5(b)(2) provides that for investigational PET drugs produced under an IND and research PET drugs produced with approval of an RDRC, the requirement under the act to follow current good manufacturing practice is met by complying with the regulations in part 212 or with USP 32 Chapter 823. We believe that PET production facilities producing drugs under INDs and RDRCs are currently substantially complying with the recordkeeping requirements of USP 32 Chapter 823 (see section 121(b) of the Modernization Act), and accordingly, we have not estimated any recordkeeping burden for this provision of the rule.

B. Batch Production and Control Records

Sections 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 produced. We also estimate that there will be a total of 173 PET drugs 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

Sections 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

Sections 212.20(c) and 212.40(a), (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

Section 212.50(f)(2) requires that any process verification activities and results be recorded. Because process verification is only 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

Sections 212.20(c), 212.60(a), (b), and (g), 212.61(a) through (b), and 212.70(a), (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 is 2,525 hours, and the annual burden for recording laboratory test results is 8,383 hours.

G. Sterility Test Failure Notices

Section 212.70(e) requires PET drug producers to notify all receiving facilities if a batch fails sterility tests. We believe that sterility test failures might occur in only 0.05 percent of the estimated 50,500 batches of PET drugs produced each year (about 25 times each year). Therefore, we have estimated that each PET drug producer will need to provide 0.25 sterility test failure notice per year to receiving facilities. The notice would be provided using e-mail or facsimile transmission and should take no more than 1 hour.

H. Conditional Final Releases

Section 212.70(f) requires PET drug producers to document any conditional final releases of a product. We believe that conditional final releases will be fairly uncommon, but for purposes of the PRA, we 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.

(Comment 44) One comment expressed concern about the estimate of the frequency of conditional final release of PET drug products. The comment noted that the preamble to the proposed rule stated that conditional final release should not be necessary except in ''very rare circumstances''; the comment also noted the statement in the preamble that 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'' within the meaning of proposed § 212.70(f)(1)(v). The comment disagreed with the estimate of one conditional final release per year for each facility, stating that there appeared to be no consideration for size or production volume. The comment maintained that the use of conditional release should be tracked by producers to look for trends in equipment failures that need corrective actions, and the diligence applied in these corrective actions should be the measure for taking reasonable efforts to ensure that the problem does not recur.

(Response) We believe that the estimate of one conditional final release per year per facility is an appropriate average number because we believe that many facilities might have no conditional final releases while others might have only a few. We agree with the comment that an assessment of ''reasonable efforts'' to prevent recurrence of a malfunction involving analytical equipment, under § 212.70(f)(1)(iv) of the final rule, would not focus primarily on the specific number of equipment failures. Instead, the reasonableness of the efforts relates to the steps that a producer takes to remedy a particular equipment problem and to identify and address trends in equipment malfunctions.

I. Out-of-Specification Investigations

Sections 212.20(c) and 212.71(a) and (b) 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 will 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.

(Comment 45) One comment maintained that the number of out-of-specification investigations is significantly underestimated (at one investigation per facility each year). The comment stated that a true failure might only occur once each year but an out-of-specification investigation is necessary each time a single item in the final product testing process results in a nonconformance to specifications. The comment stated that because quality control on each batch is executed quickly, most out-of-specification conditions are directly due to operator or equipment failure and are rectified by retesting. The comment maintained that out-of-specification investigations actually occur two to three times per month; therefore, the comment recommended that we use an estimate of 36 investigations per facility each year.

(Response) We agree with the comment's reasoning and we have revised the annual frequency of out-of-specification investigations from 1 to 36, which results in an annual hourly burden of 3,636 (101 producers times 36

investigations times 1 hour for documentation equals 3,636 hours).

J. Reprocessing Procedures

Sections 212.20(c) and 212.71(d) require PET drug producers to establish and document procedures for reprocessing PET drugs. We estimate that it will take 1 hour a year to document these procedures for each PET production facility. We did not estimate 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

Sections 212.20(c) and 212.90(a) require that written procedures regarding distribution of PET drug products be established and maintained. We estimate that it will take 1 hour annually to establish and maintain records of these procedures for each PET production facility. Section 212.90(b) requires that distribution records be maintained. We estimate that it will take 15 minutes to create an actual distribution record for each batch of PET drug products, with a total burden of 12,625 hours for all PET producers.

L. Complaints

Sections 212.20(c) and 212.100 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 will take 1 hour annually for each PET production facility and that each facility will receive one complaint a year and will spend 30 minutes recording how the complaint was dealt with.

TABLE 4.—ESTIMATED ANNUAL RECORDKEEPING BURDEN

21 CFR Section	No. of Recordkeepers	Annual Frequency of 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
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	36	3,636	1	3,636
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					90,191

TABLE 5.—ESTIMATED ANNUAL THIRD-PARTY DISCLOSURE BURDEN[1]

21 CFR Section	No. of Respondents	No. of Responses per Respondent	Total Responses	Hours per Response	Total Hours
212.70(e)	101	.25	25	1	25
Total					25

The information collection provisions of this final rule have been submitted to the Office of Management and Budget (OMB) for review, as required under section 3507(d) of the PRA. Prior to the effective date of this final rule, FDA will publish a notice in the **Federal Register** announcing OMB's decision to approve, modify, or disapprove the information collection provisions in this final rule. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

VII. Federalism

We have analyzed this rule in accordance with the principles set forth in Executive Order 13132. We have 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. Accordingly, we have concluded that the rule does not contain policies that have federalism implications as defined in the order and, consequently, a federalism summary impact statement is not required.

VIII. Effective Date

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. As stated in the proposed rule, section 121(b)(1) of the Modernization Act added this provision as a safety net while we developed the CGMP regulations for PET drugs. Section 121(b)(2) of the Modernization Act specifies that section 501(a)(2)(C) of the act will expire 2 years after the date on which we establish appropriate approval procedures and CGMP requirements for PET drugs in accordance with section 121(c)(1)(A) of the Modernization Act. For this reason, this final rule on CGMP for PET drugs will become effective 2 years after the date on which the rule is published in the **Federal Register**. (See the **DATES** section of this document.) Beginning on that date, PET drug producers will be required to produce PET drugs in accordance with the CGMP requirements set forth in part 212.

We also note that section 121(c)(2)(A) of the Modernization Act provides that we cannot require the submission of an NDA or ANDA for a PET drug until 2 years after the date on which we establish appropriate approval procedures and CGMP requirements for PET drugs. With the publication of this final rule, we have established CGMP requirements for PET drugs in accordance with section 121(c)(1)(A)(ii) of the Modernization Act. As discussed in section III.A of this document, we have established approval procedures for PET drugs in accordance with section 121(c)(1)(A)(i) of the Modernization Act. Therefore, in accordance with section 121(c)(2)(A) of the Modernization Act, the requirements in the act and FDA regulations concerning NDAs and ANDAs will become applicable to PET drugs 2 years from the date of publication of this final rule. (See the **DATES** section of this document.) After that date, PET drug producers will be required to submit either an NDA or ANDA for each of their PET drugs.

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, 21 CFR chapter I is 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 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 drugs) 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

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 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.

Component means any ingredient intended for use in the production of a PET drug, 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 malfunction involving 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 in humans.

Inactive ingredient means any intended component of the PET drug 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.

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 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 can be determined.

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

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.

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'' includes a ''PET drug product'' as defined in this section.

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

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

Production means the manufacturing, compounding, processing, packaging, labeling, reprocessing, repacking, relabeling, and testing of a PET drug.

Quality assurance means a system for ensuring the quality of active ingredients, PET drugs, 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).

Sub-batch means a quantity of PET drug having uniform character and quality, within specified limits, that is produced during one succession of multiple irradiations, using a given synthesis and/or purification operation.

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 drugs is the minimum requirements for the methods to be used

in, and the facilities and controls used for, the production, quality assurance, holding, or distribution of PET drugs intended for human use. Current good manufacturing practice is intended to ensure that each PET 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 is supposed to have.

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

(a) *Application solely to PET drugs.* The regulations in this part apply only to the production, quality assurance, holding, and distribution of PET drugs. Any human drug that does not meet the definition of a PET drug must be manufactured in accordance with the current good manufacturing practice requirements in parts 210 and 211 of this chapter.

(b) *Investigational and research PET drugs.* For investigational PET drugs for human use produced under an investigational new drug application in accordance with part 312 of this chapter, and PET drugs produced with the approval of a Radioactive Drug Research Committee in accordance with part 361 of this chapter, the requirement under the act to follow current good manufacturing practice is met by complying with the regulations in this part or by producing PET drugs in accordance with Chapter 823, ''Radiopharmaceuticals for Positron Emission Tomography—Compounding,'' May 1, 2009, pp. 365–369, 32d ed. of the United States Pharmacopeia (USP) National Formulary (NF) (USP 32/NF 27) (2009). The Director 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 a copy from the United States Pharmacopeial Convention, Inc., 12601 Twinbrook Pkwy., Rockville, MD 20852, Geeta M. Tirumalai, 301–816–8352, e-mail: *gt@usp.org,* Internet address: *http://www.usp.org/USPNF/notices.* You may inspect a copy at the Food and Drug Administration Biosciences Library, 10903 New Hampshire Ave., Silver Spring, MD, 20993–0002, 301–796–3504, 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 drug quality?

(a) *Production operations.* You must oversee production operations to ensure that each PET 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 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.

(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.

(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 mix-ups, and the prevention of contamination of equipment or product by substances, personnel, or environmental conditions that could reasonably be expected to have an adverse effect on product quality.

(b) *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, 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 drugs are not reactive, additive, or absorptive so as to alter the quality of PET drugs.

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 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 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, mix-ups, and deterioration and ensures that they are and remain suitable for their intended use.

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

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

(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 action limits 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 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;

(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 of production steps and times of critical 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 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 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 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 must keep complete records of all tests performed to ensure compliance with established specifications and standards, including examinations and assays, as follows:

(1) A suitable identification of the sample 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, and 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

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

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

(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 an appropriate laboratory determination to ensure that each batch of a PET drug product conforms to specifications, except for sterility. For a PET drug product produced in sub-batches, before final release, you must conduct an appropriate laboratory determination to ensure that each sub-batch conforms to specifications, except for sterility.

(d) *Final release procedures.* Except as conditional final release is permitted in accordance with paragraph (f) of this section, you must establish and follow procedures to ensure that each batch of a PET drug product is not given final release until the following are done:

(1) An appropriate laboratory determination under paragraph (c) 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 30 hours, 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. Tested samples must be from individual batches and not pooled. If the product fails to meet a criterion for sterility, you must immediately notify all facilities that received the product of the test results and provide any appropriate recommendations. The notification must be documented. Upon completion of an investigation into the failure to meet a criterion for sterility, you must notify all facilities that received the product of the findings from the investigation.

(f) *Conditional final release.* (1) If you cannot complete one of the required finished-product tests for a batch of a PET drug product because of a malfunction involving 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 retain a reserve sample of the conditionally released batch of drug product;

(iv) You promptly correct the malfunction of analytical equipment, complete the omitted test using the reserve sample after the malfunction is corrected, and document that reasonable efforts have been made to prevent recurrence of the malfunction;

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

(vi) 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 prevent recurrence of the malfunction involving analytical equipment.

(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 malfunction involving analytical equipment prevents

the performance of a radiochemical identity/purity test or prevents the determination of the product's specific activity.

(3) You may not release another batch of the PET drug product until you have corrected the problem concerning the malfunction of analytical equipment and completed the omitted finished-product test.

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

(a) *Rejection of 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 mix-ups. You must have and follow procedures to investigate the cause(s) of the nonconforming product. The investigation must include, but is not limited to, examination of processes, operations, records, complaints, and any other relevant sources of information concerning the nonconforming product.

(b) *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 procedures stated in the product's approved application 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 mix-ups.

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 drug 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 the quality or purity of, or possible adverse reactions to, 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 or for any other reason 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 drugs?

(a) *Record availability.* Records must be maintained at the PET drug 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 this part for a period of at least 1 year from the date of final release, including conditional final release, of a PET drug product.

Dated: December 3, 2009.

David Horowitz,

Assistant Commissioner for Policy.

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DEPARTMENT OF DEFENSE

Office of the Secretary

[DoD–2009–HA–0151; 0720–AB37]

32 CFR Part 199

Civilian Health and Medical Program of the Uniformed Services (CHAMPUS)/ TRICARE: Inclusion of Retail Network Pharmacies as Authorized TRICARE Providers for the Administration of TRICARE Covered Vaccines

AGENCY: Office of the Secretary, Department of Defense (DoD).

ACTION: Interim final rule.

SUMMARY: This interim final rule allows a TRICARE retail network pharmacy to be an authorized provider for the administration of three TRICARE-covered vaccines in the retail pharmacy setting. The three immunizations are H1N1 vaccine, seasonal influenza vaccine, and pneumococcal vaccine. In addition, this interim final rule solicits public comment on also including other TRICARE-covered immunizations in the future for which retail network pharmacies will be authorized providers. As part of DoD preparations for a possible public health emergency involving H1N1 influenza this fall and winter, this is being issued as an interim final rule.

DATES: This interim final rule is effective December 10, 2009. Written