

CHAPTER 56 - DRUG QUALITY ASSURANCE

SUBJECT: POSITRON EMISSION TOMOGRAPHY (PET) CGMP DRUG PROCESS AND PRE-APPROVAL INSPECTIONS/INVESTIGATIONS REF: 7356.002 (2/01/2002) and 7346.832 (5/10/2010)		IMPLEMENTATION DATE 12/12/2011
		COMPLETION DATE 12/11/2014
DATA REPORTING		
PRODUCT CODES	PROGRAM ASSIGNMENT CODES	
All PET Drugs Industry code: 65 Profile Class code: PET	56002P Drug Process Inspections (PET) 46832P Positron Emission Tomography (PET) Pre-Approval Inspections/Investigations (NDA) 52832P Positron Emission Tomography (PET) Pre-Approval Inspections/Investigations (ANDA)	

FIELD REPORTING REQUIREMENTS:

Establishment Inspection Reports are to be created and filed using TurboEIR using the PET-specific module.

For inspections of **routine commercial manufacturing** classified as OAI due to deficiencies of 21 CFR 212 Current Good Manufacturing Practice (CGMP) for Positron Emission Tomography Drugs, submit advisory, administrative, or judicial action recommendations via MARCS-CMS in accordance with the Regulatory Procedures Manual (RPM).

For **pre-approval inspections**, inspections should be conducted in accordance with Compliance Program 7346.832, Pre-Approval Inspections/Investigations, and this Compliance Program. As soon as the District becomes aware of any significant inspectional, analytical, or other information (such as a change in compliance status) that may affect the agency's PET drug approval decisions with respect to a firm, the District should report the information immediately according to current FACTS procedures.

If you obtain information during an inspection pertaining to inadequate adverse drug experience reporting, unapproved drug issues, or post-approval reporting violations (Annual Reports, Supplements, Field Alert Reports, etc.), report in accordance with directions provided in those applicable compliance programs and under separate captions in the EIR. Data system information about these inspectional activities should be reported using applicable separate PAC(s). Expansion of coverage under these programs into a CGMP inspection should be reported under this compliance program.

The Districts are to use this compliance program for all PET CGMP inspections.

PART I - BACKGROUND

PET is a medical imaging modality involving the use of a unique type of radiopharmaceutical drug product that contains a positron emitting isotope. The majority of PET drugs are injected intravenously into patients for diagnostic purposes. Many PET drugs are produced using cyclotrons and other production equipment at locations that are close to the patients to whom the drugs are administered (e.g., in hospitals or academic institutions). A cyclotron is a type of particle accelerator that accelerates charged particles using a high frequency, alternating voltage (potential difference) to prepare a specific radionuclide through a particular nuclear reaction. PET drug production is a related series of processes and operations that result in the preparation of a PET drug product. Major operations or steps in PET drug production typically include chemical syntheses, aseptic filling, labeling, and testing. Aseptic processing and sterility controls within the systems are critical processes and controls for coverage in the various systems. PET drugs are intended for diagnostic use and are not intended to provide a therapeutic effect; however, many PET drugs provide their diagnostic effect by binding to receptors, which is a type of pharmacological activity.

Section 121(c)(1)(A) of the FDA Modernization Act of 1997 (Modernization Act) directed FDA to establish appropriate approval procedures and CGMP requirements for PET drugs. During the development of the PET drug CGMP requirements and approval procedures, FDA evaluated and considered any relevant differences between not-for profit institutions that produce PET drugs for their patients and commercial manufacturers of PET drugs. FDA also consulted with patient advocacy groups, professional associations, manufacturers, and physicians and scientists who make or use PET drugs (as stated under section 121(c)(1)(B) of the Modernization Act). FDA presented the initial tentative approach to PET drug CGMP requirements and responded to numerous questions and comments about that approach at a public meeting on February 19, 1999. FDA announced the availability of preliminary draft regulations on PET drug CGMP requirements in the September 22, 1999 issue of the *Federal Register* (64 FR 51274). FDA held a public meeting to discuss the preliminary draft regulations on September 28, 1999. FDA announced the availability of a preliminary draft proposed rule on PET drug CGMP requirements in the April 1, 2002 issue of the *Federal Register* (67 FR 15344). FDA held a public meeting to discuss the preliminary draft proposed rule and draft guidance on April 21, 2002. FDA also announced the availability of a guidance on “PET Drug Products—Current Good Manufacturing Practice (CGMP)” on April 1, 2002 (67 FR 15404). In the *Federal Register* of September 20, 2005, FDA published a proposed rule to establish CGMP requirements for PET drugs.

The Federal Food, Drug, and Cosmetic Act provides that FDA may approve a New Drug Application (NDA), an Abbreviated New Drug Application (ANDA), and a Biologic Licensing Application (BLA) if, among other requirements, the methods used in, and the facilities and controls used for, the manufacture, processing, packing, and testing of the drug are found adequate, and ensure and preserve its identity, strength, quality, and purity.¹ Section 121(c)(2) of the Modernization Act provides that FDA cannot require the submission of a new drug application (NDA) or abbreviated new drug application (ANDA) for a PET drug product until 2 years after the day we publish a final rule establishing CGMP requirements for PET drug products. The final rule (21 CFR 212 (212 CGMP)) was

¹ Federal Food, Drug, and Cosmetic Act §§ 505(d) and 505(j)(4)(A) (21 U.S.C. §§ 355(d)(3) and 355(j)(4)(A))

published December 10, 2009 (FR 74 at 65409) with an effective date of December 12, 2011. Therefore, NDA's and ANDA's for PET drugs are required to be submitted by December 12, 2011.

In the same *Federal Register*, FDA announced the availability of a final Guidance for Industry entitled "PET Drugs—Current Good Manufacturing Practice (CGMP)" (212 Guidance). This guidance is intended to help PET drug producers better understand FDA's thinking concerning compliance with the PET 212 CGMP regulations. The guidance addresses resources, procedures, and documentation for all PET drug production facilities, academic and commercial. In some cases, the guidance provides practical examples of methods or procedures that PET drug production facilities can use to comply with the CGMP requirements. Additional information can be obtained from the FDA PET Web site (see references in Part VI).

The inspectional guidance in this program is structured to provide for efficient use of resources devoted to routine surveillance and pre-approval inspection coverage. It also provides for follow-up compliance coverage as needed.

PART II - IMPLEMENTATION

A. OBJECTIVES

The goal of this program's activities is to minimize consumers' exposure to adulterated PET drug products. Under this program, inspections and investigations, sample collections and analyses, and regulatory or administrative follow-up are made to:

- 1) determine whether inspected firms are operating in compliance with applicable 212 CGMP requirements, and if not, to provide the evidence for actions to prevent adulterated products from entering the market and as appropriate to remove adulterated products from the market, and to take action against persons responsible as appropriate;
- 2) provide a 212 CGMP assessment to determine the acceptability of a firm named in a pending new drug approval application; and,
- 3) provide input to firms during inspections to improve their compliance with regulations.

B. SCOPE

Registration and Listing: All PET drug producers are required to register and list in accordance with existing requirements and guidance, except that PET drug facilities that only produce PET drugs for research purposes under an investigational new drug application (IND) or Radioactive Drug Research Committee (RDRC) are not required to register or list.

Commercial Use: Commercial use means the use of a PET product for diagnosis not under an IND or under the review of a RDRC.

Approval: After December 12, 2011, if the PET drug is produced for commercial distribution and use in humans for clinical practice to diagnose a patient, the maker of the PET drug must have submitted a new drug or abbreviated new drug application for that drug. **A PET drug marketed prior to December 12, 2011 can continue to be marketed after the application is submitted.** (See FDA Questions and Answers documents for further information:
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/ucm085783.htm>)

PET Drug: 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. [FR 65414]

A generator system that produces a PET radionuclide from the decay of a longer half-lived parent isotope 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. As of the date of this program's issuance, FDA has approved an NDA for a PET drug containing a generator (i.e., rubidium chloride RB-82 generator). [FR 65414]

PET Active Pharmaceutical Ingredients: The PET CGMP requirements are applicable to the production of a PET API as well as the finished PET drug product containing that API. When the regulation uses the term “PET drug” it means a “**PET drug product**” as defined in § 212.1, a PET API, and other PET ingredients. The term “PET drug product” refers ONLY to a finished dosage form of a PET drug, whether or not in association with one or more other ingredients. Only certain 212 regulations apply to PET APIs (i.e., PET drugs). Please pay attention to the different uses of these terms when reviewing and applying these regulations.

PET Intermediates: 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). [FR 65414]

Investigational and Research PET Drugs: **Important Note:** 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 21 CFR 212 or the standards in USP Chapter <823>, “Radiopharmaceuticals for Positron Emission Tomography—Compounding” of the 32d ed. of the USP (2009) (USP 32). Inspections of PET drugs produced for research under the review of an RDRC, generally would be conducted on a for-cause basis only.

Practice of Pharmacy or Medicine: PET drug production includes all operations to the point of final release of a finished dosage form. The dispensing of the patient unit doses from a multidose vial (does not apply if manufacturer’s marketed product is a unit dose vial) following the release of the finished dosage form is considered the practice of pharmacy and not covered under the PET CGMP regulations. Use of a PET drug product after receipt by a receiving facility generally is regarded as the practice of medicine and pharmacy. 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. 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. [FR 65411]

Some short half-life PET drugs are individually “compounded” on-site, one dose at a time, for specific individual patients. 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. Please note that some of these PET drugs may not be required to have an approved application (see guidance: FDA Regulation of PET Products, Questions and Answers), but all are required to conform with the PET CGMP regulations.

Not for Profit: 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. 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. The PET CGMP regulations also apply to not-for-profit institutions. [FR 65413]

Additional terms are defined throughout this program if not already defined in the PET CGMP regulation at § 212.1 or related guidance.

C. STRATEGY

1) Routine Surveillance 212 CGMP Inspection of PET Producer Sites

Routine surveillance inspections evaluate whether a PET drug production facility complies with the PET CGMP regulations. The routine surveillance of PET facilities also facilitates timely decisions on the application review process and in deciding government contracts.

2) Pre-approval Inspection (PAI) of Producer Sites

A pre-approval inspection (PAI) is performed to provide assurance that a PET drug production facility that is named in a PET New Drug Application (NDA) or Abbreviated New Drug Application (ANDA) is capable of producing the PET drug in accordance with CGMPs, and that the submitted application data are reliable, accurate, and complete.

3) Compliance Inspections

Compliance Inspections are inspections done to evaluate or verify corrective actions after a regulatory action has been taken. First, the coverage given in compliance inspections must be related to the areas found previously deficient and subject to corrective actions.

The firm is expected to evaluate all of its operations and implement global corrective actions after a previously violative inspection, not just the deficiencies noted in the FDA Form 483. The Full Inspection Option should be used for a compliance inspection, especially if the Abbreviated Inspection Option was used during the violative inspection.

For Cause Inspections are compliance inspections which are done to investigate a specific problem that has come to the attention of the agency. The problems may be indicated in Field Alert Reports (FARs), industry complaints, recalls, etc.

D. PROGRAM MANAGEMENT INSTRUCTIONS

The CGMP requirements for PET drugs differ in many significant ways from the CGMP requirements for non-PET drugs found in 21 CFR parts 210 and 211. The 212 CGMP requirements include differences concerning personnel; aseptic processing; quality control of components; self-verification of production steps; same-person oversight of production; batch record

review; authorization of product release; and labeling requirements. 21 CFR 212 simplifies the requirement for testing incoming materials and components used for manufacturing and provides more flexibility in the method for determining that each batch of a PET drug product conforms to specifications before final release. The 212 CGMP provides for circumstances under which conditional final release may be acceptable. See the Guidance for Industry on 212 CGMP for PET drugs.

State of Control

A PET drug producer is considered to be operating in a state of control when it employs conditions and practices that assure compliance with the intent of Section 501(a)(2)(B) of the Act and portions of the 212 CGMP regulations that pertain to its systems. A firm in a state of control produces finished PET drug products for which there is an adequate level of assurance of quality, strength, identity, and purity.

A firm is out of control if any **one system** is out of control. A system is out of control if the quality, identity, strength, and purity of the products resulting from that/those system(s) cannot be adequately assured [21 CFR 212.2]. Documented 212 CGMP deficiencies provide the evidence for concluding that a system is not operating in a state of control. See Part V, Regulatory/Administrative Strategy, for a discussion of compliance actions based on inspection findings demonstrating out of control systems/firm.

Inspection Planning

District Offices will conduct PET drug production inspections and maintain profiles. District Offices are responsible for determining the depth of coverage given to each drug firm in accordance with this program. However, abbreviated inspections are encouraged where appropriate. Inspectional coverage in accordance with this program will provide sufficient assessment of the state of compliance for each firm. The frequency and depth of inspection should also be determined by the statutory obligation, the firm's compliance history, the technology employed, and the resources made available to inspect PET facilities. When a system is inspected, the inspection of that system may be considered applicable to all products that use it. Investigators should select an adequate number and type of products to accomplish coverage of the system. Selection of products should be made so that coverage is representative of the firm's overall abilities in production within the 212 CGMP requirements.

Inspection Teams

An inspection team (See IOM 5.1.2.5) may be composed of experts from within the District, other Districts, or Headquarters (CDER or ORA). Contact ORO/Division of Field Investigations if technical assistance or additional expertise is needed (see also FMD 142). Participation of an analyst (chemist or microbiologist) with knowledge of PET drugs on the inspection team is also encouraged, especially where laboratory issues are extensive or complex. Contact your Drug Servicing Laboratory or ORO/Division of Field Science.

Profiles

The inspection findings will be used as the basis for updating the profile class in the profile section of the FACTS EIR coversheet that is used to record profile/class determinations. All PET drug inspections should use Industry code **65** and Profile Class code "**PET**."

Note: There is only one Profile Class "**PET**" for PET drugs.

PART III - INSPECTIONAL

A. GENERAL

Review and use the 212 CGMPs to evaluate production processes. The investigator should conduct inspections according to the STRATEGY section in Part II of this compliance program.

PET Guidance for Industry documents are not to be referred to as the justification for an inspectional observation. Guidance documents do not establish requirements. They state examples of ways to meet requirements. Current Guides to Inspection and Guidance for Industry provide interpretations of requirements, which may assist in the evaluation of the adequacy of 212 CGMP systems.

Important safety notice: During an inspection of a PET manufacturing facility, the investigator will be exposed to ionizing radiation. Please refer to the IOM section 1.5.4.2.3 for additional information. It is also advisable that the investigator attend the RH102 Basic Radiation Safety training program prior to the inspection. Each investigator who visits a manufacturer of radioactive products or tests ionizing radiation emitting products must wear a Pager and a Thermo Luminescent Dosimeter (TLD) to estimate external exposure to radiation. Consult your supervisor or other District Office management for information on obtaining a Pager and TLDs.

Current inspectional observation policy as stated in the IOM says that the FDA-483, when issued, should be specific and contain only significant items. The investigation team will prepare a narrative establishment inspection report (EIR) per instructions in the IOM (Chapter 5).

Review of NDA/ANDA files may assist in selecting significant drug processes and critical process parameters for coverage in the various systems. Significant drug processes include those that contain steps with unique or difficult manipulation in the performance of a step that may affect drug quality. Aseptic processing is considered significant and should be covered. Inspections for this compliance program may be performed during visits to a firm when operations are being performed for other compliance programs or other investigations.

Unlike other commercial production facilities, PET production facilities generally employ a few operators each of whom must perform certain operations and checks quickly without disruption so that the drug product can be distributed promptly to pharmacies and waiting patients. For this reason, District Offices are to schedule PET inspections in advance with the firm to allow the facility time to ensure appropriate staff is available to enable an efficient and complete inspection. When scheduling the inspection with the firm, the investigator may obtain information about the planned times of key operations and time their arrival accordingly. "For cause" inspections need not be scheduled in advance. The investigator may also need to accommodate the typical PET establishment's early hours of operation.

B. INSPECTION APPROACHES

This program provides two options for surveillance and PAI inspections: Full Inspection Option and Abbreviated Inspection Option.

For the first two years of the program, a full inspection option is required for routine surveillance purposes (a PAI may be abbreviated). After the first two years (starting FY14), an abbreviated inspection option should be determined as described below:

1) Selecting the Full Inspection Option.

The Full Inspection Option is a surveillance or compliance inspection to provide broad and in-depth evaluation of a firm's 212 CGMP compliance. **The Full Inspection Option is an inspection of at least four of the systems, one of which must be the Quality System and include coverage of the aseptic processing controls.** Some firms may use a contract testing laboratory for microbiological tests (e.g., sterility test). In these cases, the inspection of four systems, when Laboratory Control System is selected, will comprise the inspection of the entire firm and will be considered the Full Inspection Option.

- a) Select the Full Inspection Option for an initial FDA inspection of a facility under this program.
- b) Select the Full Inspection Option when the firm has a history of fluctuating into and out of compliance. To determine if the firm meets this criterion, the District should utilize all information at its disposal, such as inspection results, results of sample analyses, complaints, DQRS reports, recalls, etc. and the compliance actions resulting from them or from past inspections. A Full Inspection may revert to the Abbreviated Inspection Option, with District concurrence, based on prior history findings of no objectionable conditions as listed in Part V in all six systems (abbreviated inspection involves auditing fewer records and evaluations).
- c) Evaluate if important changes have occurred by comparing current operations against the EIR for the previous Full Inspection. The following types of changes are typical of those that warrant the Full Inspection Option:
 - i) New potential for microbial contamination or cross-contamination arising through change in procedures or product line (e.g., new manufacturing equipment, new aseptic processing station).
 - ii) Use of new technology requiring new expertise, significant new equipment, or new facilities.
 - iii) A significant change in aseptic processing method or technique.
 - iv) A significant change in personnel at the site when there is a limited number of employees at the PET producer facility.

- d) A Full Inspection may also be conducted on a surveillance basis at the District's discretion as resources permit.
- e) The Full Inspection Option will satisfy the biennial inspection requirement.
- f) Follow up to a Warning Letter or other significant regulatory actions should generally be a Full Inspection.

2) Selecting the Abbreviated Inspection Option.

The Abbreviated Inspection Option is a surveillance or compliance inspection meant to provide an efficient update evaluation of a firm's conformance to 212 CGMPs. The abbreviated inspection will provide documentation for continuing a firm in a satisfactory 212 CGMP compliance status. Generally this will be done when a firm has a record of satisfactory 212 CGMP compliance, with no significant recalls, or product defect or alert incidents, or with little shift in the production profiles of the firm in the time since the last inspection.

The Abbreviated Inspection Option is an inspection of the Quality System and aseptic sterility controls and one additional system.

- a) This option involves an inspection of the manufacturer to maintain surveillance over the firm's activities and to provide input to the firm on maintaining and improving the CGMP level of assurance of quality of its products.
- b) An Abbreviated Inspection may revert to the Full Inspection Option, with District concurrence, based on findings of objectionable conditions as listed in Part V. However, an Abbreviated Inspection may be sufficient to justify regulatory action without the need for a Full Inspection.
- c) The Abbreviated Inspection Option is adequate for routine coverage and will satisfy the biennial inspectional requirement.

3) PAI Inspection Coverage

The PAI inspection may be covered under the Abbreviated Inspection Option

- a) The Abbreviated Inspection Option is adequate for routine coverage and will satisfy the PAI inspectional requirement.
- b) A Full Inspection may also be conducted at the District's discretion when serious non-compliance is uncovered.

C. SYSTEM INSPECTION COVERAGE

1) QUALITY SYSTEM (21 CFR 212.10, 212.20, 212.50, 212.61, 212.71, 212.100) WITH ASEPTIC STERILITY CONTROLS (21 CFR 212.30, 212.60, 212.70)

The review of the Quality System is of major importance in the manufacture of PET drugs since the drugs are produced in low volumes and typically administered prior to the completion of sterility testing. Assessment of the Quality System is performed in three phases. The first phase is to evaluate whether the quality unit has fulfilled the responsibility to review and approve all procedures related to production, quality control, and quality assurance and assure the procedures are adequate for their intended use. This also includes the associated recordkeeping systems. The second phase is to assess the data collected to identify quality problems and may link to other major systems for inspectional coverage. The third phase is to evaluate the aseptic sterility controls: sterility test results; bacterial endotoxins test performed on each production batch; integrity test of the membrane filter used for aseptic fill; environmental monitoring program (viable and non-viable monitoring and the corrective plan when action levels are exceeded); aseptic fill and media fill procedures; and growth promotion testing of microbial media [212.60(b)].

For each of the following, the firm should have written and approved procedures, and associated documentation verifying performance. The firm's adherence to written procedures should be verified through observation whenever possible. These areas are not limited to finished products, but may also incorporate components and in-process materials. These areas may indicate deficiencies not only in this system but also in other systems that may warrant more in-depth coverage. All areas under this system should be covered; however, the depth of coverage may vary depending upon inspectional findings.

- a) Production records should be reviewed, which may include investigations of non-conforming product. Records should include corrective action where appropriate.
- b) Complaints concerning quality or purity of a PET drug product, or possible adverse reactions should be documented, investigated, and followed up. Review the firm's response to any complaints.
- c) There should be a sufficient number of trained/qualified employees who have the necessary education, background, training, and experience to perform their assigned functions and to manufacture the number of batches each day. (Note: Documentation for training should demonstrate they are capable of their assigned function(s) (i.e., radiopharmacy, chemistry, and aseptic procedures needed for drug manufacture).)
- d) Change control should be approved or rejected. Change control procedures must be established and followed.
- e) Review the reprocessing records and confirm the firm followed reprocessing procedures stated in the product's approved application. If a PET drug is reprocessed, the reprocessed

batch must meet established specifications, except for sterility, before release. (Note: Typically, sterile filtration will be the only reprocessing step in the event of a failed integrity test.)

- f) Ensure the firm has a written stability testing program. [212.61] Investigate the cause of any non-conforming product. [212.71(a)]
- g) Evaluate records and written procedures for quarantined and rejected components, containers, and closures.
- h) The dispensing of patient unit doses under the practice of pharmacy is not covered under 212 CGMP. However, personnel operating in the nuclear pharmacy may also be conducting batch release or quality operations and these operations would be regulated under 212 CGMP.
- i) Evaluate whether the firm has sufficient controls to prevent administration of product to a patient by recalling a product that has been shipped before final release if it fails to conform to established specifications.

ASEPTIC STERILITY CONTROL

Inspection of the aseptic processing of the PET drug differs from that for a conventional large-scale aseptic production operation. The depth of aseptic processing coverage should be risk-based, which means focusing on the most critical process parameters and quality attributes. Aseptic processing is a critical part of PET drug production and is considered minimally required coverage for a PET inspection. In addition to the Quality System, all areas listed below should be covered; the depth of coverage should be sufficient to verify the firm is producing a safe and sterile product.

- a) Sterility Testing (Note: sterility testing must be initiated within 30 hours after completion of production and is not required to be completed prior to product release. Thirty hours may be exceeded over weekends or holiday. If the sample is held longer than 30 hours, the firm must demonstrate that the longer period does not adversely affect the sample and the test results.)
 - i) If sterility testing is performed by an outside laboratory, report the laboratory name and address.
 - ii) If sterility testing is performed in-house, assess whether the personnel are qualified to perform sterility testing and assess the results.
 - iii) The firm should have adequate written procedures for the sampling and testing of products for sterility, endotoxins, particulate matter (by visual examination), and other appropriate tests.
 - iv) Review sampling, testing, and sterility records for selected drug products. Determine if

sampling and testing were performed appropriately, and that results were within specifications (i.e., within the established acceptance criteria).

- v) Describe the firm's procedures for evaluating batches that fail the initial sterility test. How are "false positives" determined? If the cause of a sterility failure cannot be determined as arising from the production environment or laboratory error, what decision is made by the firm concerning the release of the lot in question? Is the firm taking action to correct any identified problems to prevent recurrence of a nonconforming product or other quality problem?

b) Endotoxins Testing

Determine that a bacterial endotoxins test was performed on each batch or initial sub-batch of a PET drug product. The product can be distributed under control after a pharmacopeial bacterial endotoxin test is initiated. However, the endotoxin results should meet the acceptance criteria before administering the product to humans (for further information see 212 Guidance, p. 30). 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. [212.90; 212 Guidance, p. 32; 212 Final Rule (FR), p. 65419]

For PET drugs with very short-lived radionuclides, the bacterial endotoxins test on the initial sub-batch must be completed before the release of subsequent sub-batches for human administration. [212.70(c); 212 Guidance, p. 30; 212 FR, p. 65419]

c) Dilution of the PET Drug Product Batch Vial

Evaluate that the PET drug solution obtained from a synthesizer in the final product vial assembly is diluted under sterile conditions to ensure that it meets the quality and purity characteristics it is supposed to have in the final formulation solution.

Aseptic manipulations should be performed within the aseptic hood. As such the final product vial assembly (everything that is post sterile filter and including the sterile filter) should be assembled in an aseptic hood using aseptic techniques. If a firm uses a pre-production approach and stores the assembled product vials prior to use, the maximum hold time for maintaining the sterility of the product vials should be validated. Verify that all entries into the sterile final product vial are done using aseptic technique, as follows:

i) The non-sterile side of the sterile filter can be connected to the synthesizer unit outside of aseptic hood. The dilution of the product to make the final formulated drug product solution can be performed outside of the aseptic hood through an intact sterile filter that has been pre-attached to the final product vial assembly under aseptic conditions.

ii) Alternatively, direct dilution into the sterile final product vial should be performed in an

aseptic hood.

d) Facility/ equipment and environmental controls (ref.: 212 Guidance)

If the firm uses the following equipment, it is recommended that they do the following:

i) Aseptic Workstation

When an aseptic workstation is used, it is recommended that:

1. The laminar airflow velocities be monitored periodically at the work surface as well as at the HEPA filter face to ensure adequate uniformity of flow throughout the critical area. This is typically performed during the workstation certification, but some units may measure the pressure differential of the filter to ensure appropriate airflow.
2. For aseptic equipment and facilities, the disinfectants used should be purchased sterile or sterile filtered by the firm.
3. All aseptic manipulations should be performed under environmental conditions that minimize the possibility of contamination (e.g., Class 100 in the laminar flow hood; clean and controlled environment in the hot cell).

ii) Sterilizing Filters

Evaluate how the firm is determining the integrity of the membrane filter used for aseptic fill. Filter units used to sterilize PET drugs should be subjected to the manufacturers' recommended integrity tests such as a bubble point test described in the application or SOP. The filter should be documented to be intact and not damaged. Determine that the filter integrity test was performed after completion of filtration of the PET drug product and before release of the PET drug for human administration.

When sterilizing filters are used in manufacturing PET drugs, we recommend performing the following during an inspection [see CPGM 7356.002A, Sterile Drug Process Inspections]:

1. Evaluate the firm's procedure in response to a filter that fails post-filtration testing.
2. Determine if investigations were performed following filter failures.
3. If bubble point test is used to verify the integrity of the sterilizing filter, evaluate the operator's competence in performing a bubble point test.

iii) Aseptic Filling

For PET drugs produced in batch vials, the assembly of the sealed/sterile batch production vial is performed under aseptic conditions prior to the start of manufacturing.

When encountered during an inspection, we recommend performing the following:

1. Describe in the EIR the aseptic filling processes from preparation of bulk liquid product to filling and sealing of final dosage form, including the environmental monitoring performed in critical areas during actual production.
 - (1) Evaluate the firm's environmental monitoring program. Guidance recommends that environmental monitoring of the aseptic workstation be performed periodically. In addition, it is recommended that microbiological monitoring in the aseptic workstation be conducted using settling plates during or contact plates after critical aseptic processes and sterility testing.
 - (2) Aseptic processing should be performed under environmental conditions that minimize the possibility of contamination. Evaluate if Class 100 conditions are maintained. It must be acknowledged that radiopharmaceutical "hot cells" may not be ISO classified. However, the hot cell should be a clean and controlled area. Aseptic preparation of containers and other product components (filters, syringes and needles) should be done in a Class 100 laminar flow workstation.
2. Review microbiological monitoring data for several representative months of production, including the period during which batches of the selected drug product were prepared. Verify that results were within the limits established; if results exceeded limits, evaluate firm's response.

iv) Media fill (Guidance: Media Fills for Validation of Aseptic Preparations for PET Drugs)

The media fill is a critical part of the validation to ensure the facility is capable of producing sterile PET drugs by aseptic processing.

When encountered during an inspection, we recommend performing the following:

1. Determine if the aseptic filling procedure was qualified by a media fill procedure.
2. Evaluate if the media fill simulates the aseptic processing for a routine production run. (The use of vials assembled in advance of actual fill should be evaluated under the worst-case storage period in the media fill study.) Report if

the media fill procedures were followed and the results, including:

- (1) Number of runs performed;
 - (2) Number of vials/syringes filled per run;
 - (3) Sizes of vials, syringes, and fill volume;
 - (4) Media used;
 - (5) Positive controls;
 - (6) Incubation periods;
 - (7) Incubation temperatures; and,
 - (8) Results.
3. Evaluate whether the firm investigated result of failed media fills and instituted corrective actions.
 4. Review results of media fills performed; verify that results are acceptable.
 5. Evaluate if all appropriate personnel were included in the media fill program.
 6. Evaluate the growth promotion testing of media used in the media fill simulations. It is necessary to conduct a growth promotion test on media fill media to verify that the media supports bacterial growth.

Commercially prepared media should be used within the label's shelf life and stored according to the label's recommendations. Only qualified vendors should be used.

7. Incoming environmental monitoring plates should be checked to confirm identity and physical integrity upon receipt. Only qualified vendors should be used.
8. Review the temperatures and incubation time records used to incubate media fill samples.
9. Evaluate whether the microorganisms from positive vials were identified according to genus.
10. Evaluate if the firm determines that such microorganisms correlated to those found during environmental monitoring.

2) FACILITIES AND EQUIPMENT SYSTEM (21 CFR 212.30)

When this system is selected for coverage, all areas listed below should be covered; however, the depth of coverage may vary depending upon inspectional findings. For PET facilities typically the same area or room may be organized for multiple operations, such as manufacturing, laboratory, and aseptic controls. The same individuals may be performing multiple operations.

The dispensing of patient unit doses under the practice of pharmacy is not covered under 212 CGMP. However, personnel operating in the nuclear pharmacy may be conducting batch release or quality operations and these operations would be regulated under 212 CGMP.

This system includes the measures and activities which provide an appropriate physical environment and resources used in the production of the PET drug. It includes:

- a) Facilities adequate to ensure the orderly handling of materials and equipment, prevention of mix-ups, and prevention of contamination of equipment or product (see 212 Guidance, VI.B, p. 8).
- b) Equipment procedures for maintenance, cleanliness, suitability for intended purposes. Equipment should be properly installed, maintained, and capable of repeatedly producing valid results (see 212 Guidance: VI.C.1, p. 10). Activities in accordance with procedures must be documented.
- c) Equipment construction and maintenance contact surfaces are not reactive, additive, or absorptive.
- d) The firm's adherence to written procedures should be verified through observation whenever possible. These areas may indicate deficiencies not only in this system but also in other systems that would warrant more in depth coverage.
- e) Although the cyclotron is included in the definition of a PET drug, the cyclotron used to manufacture the radioisotopes for PET drugs is not to be physically inspected due to the complexity of the instrumentation and health hazards. The maintenance records of the target window (including target window rebuild) may be reviewed to identify problem encountered, and corrective actions. Normally, attention is devoted to this issue if a quality problem has been identified.
- f) All testing, measuring, monitoring equipment (e.g., thermometer, thermocouple systems, pressure gauges, pH meter) used in production should be maintained and calibrated (212 Guidance: VI.C, p. 10). This would include the automated radiochemical synthesis unit that is used to produce the PET drug product. Depending on the application and the process, certain production equipment may be of single use, such as resin cartridges used in purification. In some applications, the connective tubing may be single use and must be replaced for each production run.
- g) Checked to ensure cleanliness and suitability immediately before use. Records of these checks must be kept

PET Drug Generator Systems

The use of nuclide generators, such as ^{82}Rb or ^{62}Cu generator, may pose special concerns. When encountered during an inspection, we recommend reporting the following information:

1. Quality control procedures used in the assembly, testing and re-use of the generator-system regarding the following areas:
 - (1) Assay;
 - (2) Calibration;
 - (3) Sterility;
 - (4) Endotoxins control;
 - (5) pH;
 - (6) Contaminants (radioactive and non-radioactive) eluting from the generator;
 - (7) Reproducibility of daily elution pattern; and,
 - (8) Evaluation of parent radioisotope breakthrough at the end of elution to ensure levels are within the recommended limits.
2. Any use of bacteriostatic agents in the preparation of eluting solutions.
3. Instructions provided the user as to the assembly, operation and maintenance of sterility.
4. Determine the manufacturer of the generator and the source and purity of the radioactive materials used.

3) MATERIALS SYSTEM (21 CFR 212.10, 212.20, 212.40)

This system includes measures and activities to control finished products, components, including water or gases that are incorporated into the product, containers and closures. It includes inventory control processes, drug storage, distribution controls, and records.

The firm must have written procedures describing the receipt, log-in, identification, storage, handling, testing, and acceptance or rejection of components and containers and closures. The procedures must be adequate to ensure that they are suitable for their intended use. The firm's adherence to written procedures should be verified through observation.

Note: Only certain 212 regulations apply to PET APIs, as indicated herein.

In addition to the Quality System and aseptic sterility controls, when this system is selected for coverage, all areas listed below should be covered; however, the depth of coverage may vary depending upon inspectional findings.

- a) Inert gases are commonly used to pressurize the chemical synthesis unit and facilitate the flow of components. The gases may also be used for the evaporation of solvents. These gases come in contact with the drug product and should be filtered.
- b) Component, container, and closure suppliers are qualified.
- c) Components are handled and stored in a manner that prevents contamination, mix-ups, and

deterioration.

- d) Storage under quarantine until tested or examined and released.
- e) For containers and closures: Representative samples of each lot must be examined for conformity to written specifications. A visual identification is required of each lot.
- f) If finished product testing is not conducted that ensures that the correct components have been used, at least one identity test must be conducted on each lot of each component that yields an active ingredient and each lot of an inactive ingredient used in that PET drug product. Note: If a PET facility uses an inactive ingredient that is an approved product and marketed as a finished drug product intended for intravenous administration (for example, sterile saline), then an identity test on an inactive ingredient is not required. Refer to 21 CFR 212.40 (c) (1) (ii).
 - i) For solvents or reagents, that are not the subject of finished-product testing, it must be determined that each lot complies with written specifications by examining a certificate of analysis provided by the supplier.
 - ii) If a component is used to prepare an inactive ingredient on site, then an identity test must be performed on the components used to make the inactive ingredient before the components are released for use.
 - iii) Appropriate retesting/reexamination of components.
- g) If finished product testing is conducted to ensure that the correct components were used, then each lot of components must comply with written specifications by examining a certificate of analysis, and an identity test is not required.
- h) Components, containers, and closures appropriately designated (i.e., quarantined, accepted, or rejected).
- i) Control system for implementing changes in the materials handling operations to include demonstrating that any change does not adversely affect the identity, strength, quality, or purity of a PET drug.
- j) Documented results of any investigation.
- k) Components, containers, and closures include:
 - i) Closures, syringes, needles, tubing, etc.
 - ii) Packaging materials.
 - iii) Chemicals and other raw materials used in manufacturing, such as saline solution, buffers, radiochemicals, kits for chemistry stations, etc.

iv) Radionuclides (radioactive isotopes).

4) PRODUCTION SYSTEM (21 CFR 212.10, 212.20, 212.50, 212.70)

This system includes measures and activities to control the production of PET drugs including batch production, in-process sampling and testing, and process verification, if required. It also includes establishing, following, and documenting performance of approved production procedures.

Note: Production includes all operations to the point of final release of a finished dosage form. The use of a PET drug product after receipt by a receiving facility generally is regarded as the practice of medicine and pharmacy. [212 FR, p. 65411]

Note: PET CGMPs distinguishes batches from sub-batches for requirements related to process verification and conformance to specifications.

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. Exceeding the radiochemical yield limits would require investigation and corrective action but not necessarily rejection of the batch. [212.50; 212 Guidance, p. 19; 212 FR, p. 65416]

PET drug product specifications consist of critical and non-critical (or key) attributes. Measurements of critical quality attributes are essential because they are indicative of the product's safety and effectiveness. Examples of critical attributes include appearance, radiochemical identity and purity (including chiral purity when applicable), assay (including radioconcentration), specific activity (the radioactivity at a specific time per unit mass of the element or of the chemical in the PET drugs in mCi/ug or mCi/umole), radioactive and non-radioactive impurities, pH, bacterial endotoxin, and membrane filter integrity.

However, 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. [212 FR, p. 65418]

The firm should have written and approved procedures and documentation to ensure that all key process parameters are controlled and that any deviations are justified. The firm's adherence to written procedures should be verified through observation whenever possible. In addition to the Quality System and aseptic sterility controls, when this system is selected, all areas listed below should be covered; however, the depth of coverage may vary depending upon inspectional findings.

- a) Process changes should be approved before they are implemented. Change control procedures must be established and followed.
- b) Reprocessing a batch is only appropriate if reprocessing procedures are stated in the product's approved application.
- c) Identification of all major equipment used in production
- d) Master production and control records that document all steps in the production process

Note: Reasonable variations are permitted in the amount of component necessary if they are specified in the master production and control records (212.50(b)(5)).

- e) 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. Batch records may be stored either in hard copy or on the firms' computer system or network. The batch record should provide complete traceability to the lots used in the batch production, and identify procedures used and personnel involved in the performance of each critical step and in the testing and approval of a batch.

- f) Production area and equipment is clean and suitable for use
- g) Control of in-process materials until testing/verification activities have been completed or approvals are received and documented
- h) Process verification
 - i) For a PET drug for which each entire batch undergoes full finished-product testing to ensure that the product meets all specifications, process verification is not required.
 - ii) 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.

- i) Production records must be reviewed by the person responsible for QA to determine if errors have occurred.
- j) Production components (ref.: 212 Guidance)

If certain components (e.g., ion exchange columns / cartridges) are preassembled in bulk for use over a period of time, then make sure their production and storage conditions are appropriate to prevent microbial growth and contamination.

If production is performed using different chemical synthesis equipment, verification studies should be performed for each type of equipment.

5) PACKAGING AND LABELING SYSTEM (21 CFR 212.10, 212.20, 212.50, 212.80)

This system includes measures and activities that control the packaging and labeling of PET drugs and drug products. It includes label examination [212.80(b)], storage, handling, distribution and use, and controls to prevent labeling and product mix-ups.

In addition to the Quality System and aseptic sterility controls, when this system is selected for coverage, all areas listed below should be covered; however, the depth of coverage may vary depending upon inspectional findings.

- a) Packaging and labeling changes should be approved or rejected. Change control procedures must be established and followed.
- c) The product should be packaged and labeled to protect the product from alteration, contamination, and damage.
- d) Labels must be applied so they remain legible and affixed during the conditions of processing, storage, handling, distribution, and use.
- e) Master production and control records must include a description of containers, closures, packaging materials, and contain a specimen or copy of each label and all other labeling.
- f) The batch production record must include labeling.
- g) Packaging and labeling operations must be controlled to prevent mix-ups (i.e., examination and reconciliation of issued labels).

6) LABORATORY CONTROL SYSTEM (21 CFR 212.10, 212.20, 212.60, 212.61, 212.70)

This system includes measures and activities related to laboratory procedures, sampling, testing, analytical methods development and verification, and the stability program.

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. 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 information needed to identify a sample might vary depending on the circumstances under which production and testing are conducted. [212 FR, p. 65417, comment 29]

For each of the following, the firm should have written and approved procedures for the conduct of each test, and documentation of the results. The firm's adherence to written procedures should be verified through observation whenever possible. In addition to the Quality System and Aseptic Sterility Controls, when this system is selected for coverage, all areas listed below should be covered; however, the depth of coverage may vary depending upon inspectional findings.

- a) Methods, specifications, and procedure changes should be approved before they are implemented. Change control procedures must be established and followed.
- b) Procedures should ensure that laboratory equipment is clean, suitable for its intended purposes, properly installed, maintained, and capable of repeatedly producing valid results. Activities must be documented in accordance with these procedures.
- c) Procedures should be written to ensure that laboratory equipment is routinely calibrated, inspected, and maintained. The activities must be documented in accordance with these procedures.
- d) Determine that sampling and testing procedures ensure that components and in-process materials conform to appropriate standards.
- e) Complete analytical records from all tests and statement of the results of tests including the date and time the test was conducted. Documentation should include a statement that the test results compare with established acceptance criteria.
- f) Establishment of a written stability testing program for each finished PET drug product, including reliable, meaningful, and specific test methods (212.61; note that APIs and other components of PET drugs are not subject to this regulation). The stability samples must be representative of the lot or batch from which they were obtained and should be checked to verify conformance to the approved drug application stability conditions (see 212 Guidance, p. 27). The radioconcentration (at end of synthesis) of the batches routinely produced should be below the radioconcentration (at end of synthesis) of the batches tested for stability.
- g) Refer to the specific compendia requirements and approved application for the PET drug product requirements for final release. These tests may include microbiological, chemical, endotoxins, and radionuclidic and radiochemical identity and purity tests performed.
- h) Evaluate method validation and/or verification. When a test method is developed at a site other than the production and testing facility, as is often the case for multi-site firms, the

method transfer and verification protocol and report should be evaluated.

Notes: For conditional final release [212.70(f)], if a malfunction prevents the performance of a radiochemical identity/purity test or prevents the determination of the product's specific activity, the product must not be released.

Conditional final release may be appropriate 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 [212.70(f); 212 FR, p. 65420, comment 34].

Further background information is provided for easy reference:

1. 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. Laboratory tests for critical product attributes must be completed before final release. Conditional final release must not be approved 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.
2. However, a PET drug producer may allow conditional final release if the PET drug producer cannot complete one of the required finished-product tests for a non-critical attribute of a PET drug product because of a malfunction involving analytical equipment, rather than solely a complete breakdown of such equipment. Conditional release should be extremely infrequent and meets the criteria as specified in the PET CGMP regulations (§ 212.70(f)(1)).
3. 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. Or, for example, a PET drug producer might observe a baseline drift in 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.
4. A reserve sample must be retained of the conditional release batch.
5. If an out-of-specification result is obtained when testing the reserve sample, the firm must immediately notify the receiving facility.

6. The firm must document all testing, notifications, and corrective actions to prevent recurrence involving the malfunction of the analytical equipment.
 7. Another batch of PET product must not be released until the problem is corrected concerning the malfunction and the omitted finished product test is completed.
 8. It is not appropriate 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. It is not appropriate to allow each PET drug producer to determine which finished product tests may be omitted under conditional final release. It is not 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.
 9. As for radionuclidic purity, 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.
- h) The identity, purity, and quality of reagents, solutions and supplies used in testing procedures must be adequately controlled and properly labeled with expiration dates. Where appropriate, a CoA for each lot of incoming material should be inspected against the firm’s current specification (refer to materials section). Verify the appropriate storage and use of the reagents according to the manufacturer’s expiration date.
 - i) Determine that analytical methods are suitable for their intended use and are sufficiently sensitive, specific, accurate, and reproducible.
 - j) Ensure test records are complete in accordance with 212.60(g).
 - k) All instruments used in laboratory operations should be identified. Any changes in instrumentation should be noted on successive inspections.
 - l) Laboratory Equipment typically seen in PET facilities:
 - i) High-Performance Liquid Chromatograph (HPLC)

If the firm chooses to use an HPLC, it is recommended that they do the following:

1. That the HPLC system has detectors suitable for the intended purpose and be of sufficient sensitivity. Generally UV and radiochemical detectors are used. Ensure that the radiochemical detector is used within the specified operating range.
2. That prior to each day of use, the analysts perform a system suitability test (212 Guidance, p. 13)
3. That the column be stored in a suitable solvent that is compatible with the column and will inhibit microbial growth. Refer to the drug application for specific details.

ii) Dose Calibrator

It is an appropriately calibrated ionization chamber used to measure the total amount of radioactivity in a PET drug to be administered to a patient. To assure that dose calibrator is reading correctly, see the manufacturers' instructional manual (see 212 Guidance, p. 14).

iii) Radiochromatographic Scanner

It is used to measure radiochemical purity. Radiochemical purity is that proportion of the total radioactivity that is present in the desired chemical form of the radioactive substance in the PET drug. Typically, a PET drug producer will use a radiochromatographic scanner to measure the radioactivity distribution in a developed thin layer or paper chromatographic medium. It is recommended that they follow the manufacturers' recommended checks and maintenance (212 Guidance, p. 14).

iv) Multichannel Analyzer (MCA)

It is used to measure radionuclidic purity and identity. Radionuclidic purity is that proportion of the total radioactivity present in the specified radionuclide of the radioactive substance in the PET drug at a specific time. Typically, a PET drug producer will use a MCA (212 Guidance, p. 14).

v) Gas Chromatograph (GC)

It is used to measure residual solvents in the drug product (212 Guidance, p. 13).

PART IV - ANALYTICAL

A. ANALYZING LABORATORIES

No analytical activities are planned under this program. It is not anticipated that samples will normally be collected for PET radioisotopes; however, for-cause investigations may require sampling. Refer to the for-cause assignment for instructions on sampling, if any.

PART V - REGULATORY/ADMINISTRATIVE STRATEGY

Inspection findings that demonstrate that a firm is not operating in a state of control may be used as evidence for taking appropriate advisory, administrative and/or judicial actions. When it is consistent with the public protection responsibilities of the agency and the nature of the violation is significance, formal agency regulatory actions will be recommended.

The instructions outlined in the Regulatory Procedures Manual (RPM) should be followed. Regulatory recommendations must be submitted to CDER, Office of Compliance, Division of Manufacturing and Product Quality (DMPQ) via electronic copy (e.g., doc, pdf files, etc.) using the “Mission Accomplishment and Regulatory Compliance Services-Compliance Management Services” (MARCS-CMS) link located on the Inside FDA’s IT Application Page under ORA Applications.

Regulatory options include Warning Letters, injunctions and prosecutions. In most cases, seizure or recall of small batches of short-lived radioactive drug products will not be feasible because they are dispensed so quickly. Refusal to approve (21 CFR 314.125 or 314.127) or withdrawal of approval (21 CFR 314.150) of an NDA or a supplemental NDA is an additional option.

The District Office will consider all of the inspectional, analytical, administrative, voluntary and regulatory follow-up options available when a violative situation is encountered. When deciding the type of action to recommend, the initial decision should be based on the significance of the violation(s), the firm’s compliance history and the most effective way to protect consumers. The District Office should proactively initiate regulatory discussions with CDER/OC/DMPQ and the Office of Enforcement prior to the formal submission of a regulatory recommendation.

A. REGULATORY ACTION

- 1) The following should be used in recommending an appropriate regulatory action to CDER/OC/DMPQ:

Under section 501(a)(2)(B) of the act, a PET drug is adulterated unless it is produced in compliance with 21 CFR 212.

Exceptions: Provisions of USP Chapter <823> apply when PET drugs are produced under:

- Investigational New Drug Application (IND)
- Radioactive Drug Research Committee (RDRC)

- 2) Major deviations from CGMPs

Evidence to support significant and/or a trend of deficiencies within a system covered could demonstrate the failure of a system and should result in consideration of the issuance of a Warning Letter, Untitled Letter, or other judicial action by the District. When deciding the type

of action to recommend, the initial decision should be based on the risk to the public health and/or the frequency of the problem.

Districts should prepare and submit an advisory or judicial action recommendation for any firm that demonstrates serious violations causing their products to be adulterated under section 501(a)(2)(B) of the Act [21 USC ~ 351(a)(2)(B)]. Significant violations are outlined below:

- a) Failure to reject a batch of PET drug product that did not conform to specifications [212.71(a)]
- b) Failure to establish finished product release specifications [212.70(a)]
- c) Failure to complete finished product testing (except for sterility) for final release [212.70(c)]
- d) Release and distribution of product that does not meet specifications [212.70(d)]
- e) Failure to establish a written stability testing program for each finished PET drug product [212.61(a)]
- f) Failure to establish master and/or batch production and control records [212.50(b) and (c)]
- g) Significant facilities or equipment deficiencies impacting aseptic filling conditions and/or product safety and quality [212.30(a) and (b)]
- h) Failure to utilize the appropriate sterilizing filter to ensure quality and purity [212.20(a)]
- i) Failure to perform an integrity test on the membrane filter used for aseptic fill [212.50(c)]
- j) Failure to investigate batches that fail the sterility test [212.70(e)]
- k) Failure to notify all facilities that received product that failed to meet sterility [212.70(e)]
- l) Failure to perform a bacterial endotoxins test on each batch or initial sub-batch of a PET drug product [212.70(a) and (c)]
- m) Failure to perform media fills for the aseptic filling procedure as appropriate to ensure product quality and purity [212.50]
- n) Failure to evaluate the generator to ensure that the parent radioisotope breakthrough is within the recommended product quality and purity specifications [212.50]
- o) Failure to perform growth promotion testing (i.e., media supports bacterial growth) at prescribed time points [212.60(b)].

PART VI - REFERENCES, ATTACHMENTS, AND PROGRAM CONTACTS

A. REFERENCES:

- 1) PET CGMP regulations: Code of Federal Regulations, Title 21, Part 212
- 2) PET CGMP Final Rule: Federal Register: December 10, 2009 (Volume 74, Number 236), Page 65409-65436 (includes preamble and general comments explaining the final PET CGMP regulations)
<http://www.regulations.gov/#!documentDetail;D=FDA-2004-N-0449-0003>
- 3) Guidance: PET Drugs – Current Good Manufacturing Practice (CGMP)
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070306.pdf>
- 4) Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing
<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064971.htm>
- 5) Basic Radiation Safety Course, RH102 (FDA/ORR, Division of Human Resource Development (DHRD) (see IOM section 1.5.4.2.3)
- 6) Guidance: FDA Regulation of PET Products: Questions and Answers
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/ucm085783.htm>
- 7) Guidance: Media Fills for Validation of Aseptic Preparations for PET Drugs
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM273766.pdf>

B. PROGRAM CONTACTS**ORA**

ORO/Division of DOMESTIC Field Investigations/Drug Group (HFC-132)

Telephone: (301) 796-5403

ORO/Division of Field Science (HFC-140)

Telephone: (301) 796-5955

Center for Drug Evaluation and Research

CGMP Questions and Product Quality Problems (NDA/ANDA/Compendial Specifications deviations)

For a current list of OMPQ's Compliance Program contacts, please refer to CDER's "[CGMP Subject Matter Contacts](#)" (this list is posted at www.fda.gov). This list also includes subject matter contacts for manufacturing and product quality areas.

Telephone: 301-796-3120

PART VII - CENTER RESPONSIBILITIES

CENTER FOR DRUG EVALUATION AND RESEARCH

The Office of Manufacturing and Product Quality (OMPQ) will conduct periodic evaluations in order to assess the effectiveness of this program.

Please send any comments on the operation and efficiency and direct any questions regarding application of the program to the Quality Management System (QMS). The QMS complaint and feedback form should be the appropriate response for feedback on efficiency or operation of this program.