

**PRELIMINARY DRAFT REGULATIONS ON CURRENT GOOD MANUFACTURING  
PRACTICES FOR PET DRUGS**

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

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

Subpart A--General Provisions

§ 212.1 What is the meaning of the technical terms used in these regulations? **[NOTE: MAY NEED TO ADD DEFINITIONS OF "ACTIVE INGREDIENT," "PET CENTER," AND "PRESCRIPTION"]**

(a) 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.

(b) Act means the Federal Food, Drug, and Cosmetic Act, as amended (21 U.S.C. 301 et seq.).

(c) 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 manufacturing order during the same cycle of manufacture.

(d) 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 as well as any packaging materials and container-closure systems.

(e) Compounded positron emission tomography (PET) drug means a PET drug that has been compounded by or on the order of a practitioner who is licensed by a State to compound or order compounding for a PET drug and is compounded in accordance with that State's law, for a patient or for research, teaching, or

quality control.

(f) Drug product means a finished dosage form that contains a PET drug, generally, but not necessarily in association with one or more other ingredients.

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

(h) Lot number, control number, or batch number means any distinctive combination of letters, numbers, or symbols from which the complete history of the compounding, manufacturing, processing, packing, holding, and distribution of a batch or lot of PET drug product, or target material used specifically in the preparation of PET drugs can be determined.

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

(j) Percentage of theoretical yield means the ratio of the actual yield (at any appropriate phase of production of a particular drug product) to the theoretical yield (at the same phase), stated as a percentage.

(k) Positron emission tomography (PET) drug means a drug that exhibits spontaneous disintegration of unstable nuclei by the emission of positrons and is used for the purpose of providing dual photon positron emission tomographic diagnostic images, and 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.

(l) Production means the compounding, manufacturing, processing, packaging, labeling, remanufacturing, repacking, relabeling, and testing of a PET drug.

(m) Quality control means a system for maintaining the quality of drug substances, drug products, intermediates, raw materials, analytical supplies, and other components, including container-closure systems and in-process controls, through procedures, tests, analytical methods and acceptance criteria.

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

(o) Receiving facility means any PET center, hospital, institution, imaging facility, or other entity that accepts a compounded PET drug for human use. A receiving facility may be in a different department but physically located in the same building as the PET center.

(p) Release means the authoritative decision to permit the use of a component, container and closure, in-process material, packaging material, or labeling in the production of PET drugs and to permit the use of a batch of finished PET drug product for patient administration.

(q) Strength means the concentration of the drug substance (radioactivity amount per volume at the time of initial assay).

(r) Theoretical yield means the quantity that would be produced at any appropriate phase of production of a particular drug product, based on the quantity of components to be used, in the absence of any loss or error in production.

(s) Validation means confirmation by examination and provision of objective documented evidence that the particular requirements for a specific intended use can be consistently fulfilled.

(t) Verification means confirmation by examination and provision of objective evidence that specified requirements have been fulfilled.

(u) You or I mean any person who engages in the activities related to production and/or distribution of PET drugs for use in humans.

§ 212.2 What are current good manufacturing practices for PET drugs?

(a) Current good manufacturing practices for PET drug

products are the minimum requirements for the methods to be used in, and the facilities and controls used for, the production, quality control, holding, or distribution of a safe and effective PET drug product intended for human use.

(b) Current good manufacturing practices for PET drug products must include certain factors that are adequate 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. These are:

- (1) personnel and resources;
- (2) quality control systems;
- (3) equipment and facilities;
- (4) control of components, in-process materials, and finished product;
- (5) production and process controls;
- (6) laboratory controls;
- (7) acceptance criteria;
- (8) labeling and packaging controls;
- (9) distribution controls;
- (10) complaint handling; and
- (11) record keeping.

#### 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 enable them to perform their assigned functions correctly, and the resources, including equipment and facilities, to enable them to perform their functions.

#### Subpart C--Quality Control

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

(a) You must have a quality control unit that can oversee production operations to ensure that a quality PET drug is produced.

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

(c) The quality control unit must also be able to approve or reject procedures or specifications and any changes to a specification, method, process or procedure that affect the identity, strength, quality, or purity of a PET drug product before they are implemented. It must also assess the need for revalidation after a change has been made.

(d) The quality control unit must also have authority to review production records to determine whether errors have occurred. If errors have occurred, or a production batch or its components fails to meet any of its specifications, the quality control unit must ensure that the errors or failures have been fully investigated and corrective action taken.

(e) To ensure that the responsibilities of the quality control unit are known to all involved in PET drug production, the responsibilities of the unit and the procedures they will

follow must be in writing and followed.

Subpart D--Equipment and Facilities

§ 212.30 What requirements must my equipment and facilities meet?

(a) You must provide adequate facilities to assure the orderly handling of materials and equipment, the prevention of mix-ups, and the prevention of contamination of equipment or product by substances, personnel, or environmental conditions that could reasonably be expected to have an adverse effect on product quality.

(b) You must ensure that all equipment that could reasonably be expected to adversely affect the strength, quality, or purity of a PET drug, or give erroneous or invalid test results when improperly used or maintained, is clean, suitable for its intended purposes, properly installed, maintained, and capable of repeatedly producing valid results. These activities must be documented.

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

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

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

(c) Upon receipt, each lot of components and containers and closures must be uniquely identified and examined to determine whether it complies with specifications. Any lot that does not meet its specifications, including any expiration date if applicable, or that has not yet been released must not be used in PET drug production. Any lot that meets specifications must be marked "approved."

(1) At least one test must be conducted on each lot to verify the identity of each component. Specific identity tests must be used if they exist.

(2) A representative sample of each lot of each component, and each container and closure, must be tested for conformity to its written specifications. Instead of such testing a report of analysis may be accepted from the supplier provided the PET

center establishes the reliability of the supplier's test results, performs at least one specific identity test on each lot of a component, and conducts at least a visual identification of each lot of containers and closures.

(d) Components and containers and closures must be handled and stored in a manner that prevents contamination, mix-ups, or deterioration and ensures that these are suitable for their intended use.

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

#### Subpart F--Production and Process Controls

§ 212.50 What types of production and process controls must I have?

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

(b) Adequate production and process controls must include written production and process control procedures, master and batch production and control records, and validation of the production process and controls.

(c) Written production and process control procedures must include a master production and control record that documents all steps in the drug production process. The procedures must also ensure and document that key process parameters are controlled and deviations from the procedures are documented and justified. Master production and control records must include:

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

(2) The name and weight or measure of each active ingredient per dosage unit or per unit of weight or measure of the drug product, and a statement of the total weight or measure of any dosage unit;

(3) A complete list of components designated by names or codes sufficiently specific to indicate any special quality characteristic;

(4) An accurate statement of the weight or measure of each component, using the same weight system (metric, avoirdupois, or apothecary) for each component. Reasonable variations may be permitted in the amount of component necessary if they are justified in the master production and control record.

(5) A statement of theoretical yield, including the maximum and minimum percentages of theoretical yield beyond which investigation is required;

(6) Complete manufacturing and control instructions, sampling and testing procedures, specifications, special

notations, and precautions to be followed; and

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

(d) Each time a batch of PET drug is produced a unique batch production and control record must be prepared. The batch production record must identify by number or other unique identifier the specific batch that was produced, and include each production step (obtained from the approved appropriate master production or control record), actual weights of components used, dates, testing results, labeling, and names (initials or signatures) of persons performing or checking each significant step in the operation and any investigations conducted.

(e) The production and dispensing area and all equipment must be inspected to ensure cleanliness and suitability immediately before use. Activities must be documented.

(f) 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.

(g) The process for producing each PET drug (including the computers or automated data processing systems used as part of production) must be validated according to established procedures, and the quality control unit must approve both the

validation process and the results of each validation activity. Validation activities and results must be documented. Documentation must include the date and signature of the individual(s) approving the validation, the monitoring and control methods and data, and the major equipment validated.

(h) For thirty days after the date on which you manufacture a batch of a PET drug, you must keep a reserve sample from the batch that is sufficient to perform two tests.

#### Subpart G--Laboratory Controls

§ 212.60 What types of requirements apply to the laboratories that I use to conduct testing of components, in-process materials, and finished PET drug products?

(a) Each laboratory used to conduct testing of components, in-process materials, and finished PET drug products must have and follow written procedures for the conduct of each test and for the documentation of the results.

(b) Each laboratory must have scientifically sound sampling and testing procedures designed to assure that components, drug product containers and closures, in-process materials, and PET drug products conform to appropriate standards, including standards of identity, strength, quality, and purity, when such standards exist.

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

accurate, and reproducible.

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

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

(f) 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) Each laboratory performing tests related to the production of a PET drug product must keep complete records of all tests necessary to ensure compliance with established specifications and standards, including examinations and assays, as follows:

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

(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 measure of the sample

used for each test.

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

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

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

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

(a) You must establish, follow, and maintain a written testing program to assess the stability characteristics of PET drug products. This stability program must include suitable storage conditions as well as the use of reliable, meaningful and specific test methods.

(b) The results of such stability testing must be documented and used in determining appropriate storage conditions as well as expiration dates and times.

Subpart H--Finished Drug Product Controls and Acceptance Criteria

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

(a) For each batch of drug product, you must establish

acceptance criteria for the drug product including criteria for identity, strength, quality, purity, and, if appropriate, sterility. You must ensure that each batch of PET drug product meets its established acceptance criteria, except for sterility, before it is released.

(b) Sterility testing need not be completed before release but must be started as soon as possible after production. If the product fails the sterility test, the results must be immediately communicated to all receiving facilities, with appropriate recommendations and follow-ups. In addition, the doctor who wrote the prescription for the PET drug must be notified. Such notifications must be documented.

(c) You must conduct laboratory testing to demonstrate that each PET drug product meets the acceptance criteria before release of the drug product. You must establish and document the accuracy, sensitivity, specificity, and reproducibility of the test methods.

(d) You must establish and follow procedures to ensure that the PET drug product is not released until:

- (1) Appropriate laboratory testing is completed;
- (2) Associated laboratory data and documentation are reviewed; and

(3) Release is authorized by the dated signature of a designated, qualified individual.

(e) You must reject drug products that fail to meet acceptance criteria. You may perform reprocessing if appropriate. If the material is reprocessed, you must follow pre-established procedures (see production and process controls) and the finished product must meet acceptance criteria before release.

§ 212.71 What other actions must I take if a batch of PET drug product does not meet the acceptance criteria?

(a) If a batch of PET drug product does not meet the acceptance criteria, you must notify the quality control unit, and identify and segregate the product to avoid mix-ups. You should have and follow procedures to investigate the cause(s) of the nonconforming product. Such an investigation must include, but is not limited to, examination of processes, operations, records, complaints, and any other relevant sources of information concerning the nonconforming product.

(b) You must document any investigation for a PET drug product that does not meet acceptance criteria and include what happened to the rejected PET drug product.

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

Subpart I--Labeling and Packaging

§ 212.80 What are the requirements associated with labeling and

packaging PET drug products?

(a) You must assure that packaging and shipping containers are designed and constructed to protect against alteration or damage during the established conditions of storage, handling, distribution, and use.

(b) Each PET drug product must be labeled with the name of the product, its strength, the batch number or other unique batch identifier, the date and time it was prepared, and an expiration date and time determined by appropriate stability testing.

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

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

(e) All information from each label must be contained in each batch production record.

#### Subpart J--Distribution

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

(a) You must establish, maintain, and follow procedures for the control of distribution of PET drug products shipped from the PET center to ensure that only those products approved for release are used, that prescriptions are reviewed to assure that they have been properly filled, and that the process of shipping

will not adversely affect the quality, purity, and identity of the PET drug product.

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

(1) The name and address 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 patient's prescription, if applicable, or any control number(s) used; and

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

#### Subpart K--Complaint Handling

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

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

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

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

number, the name of the complainant, the date the complaint was received, the nature of the complaint, and the response to the complaint. It must also include the findings of any investigation and follow-up, or a reason why no investigation was conducted and the name of the person who determined this.

(d) A PET drug product that is returned because of a complaint may not be reprocessed and must be destroyed.

#### Subpart L--Records

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

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

(b) You must maintain all records and documentation referenced in other parts of this regulation for a period of no less than 3 years from the date of release of a PET drug product.