Template Provided By:

Cancer Imaging Program

National Cancer Institute

Standard Operating Procedure

GEN-Q012

Quality Systems Administration

1. **PURPOSE:** To give an overview of the quality systems implemented within the *Sponsor's Program* for the manufacture of radiopharmaceuticals under investigational new drug applications.

2. **SCOPE:** This quality systems plan encompasses the oversight of all documented manufacturing activities conducted under the investigational new drug applications held by the *Sponsor*.

3. **RESPONSIBILITIES**

   3.1. Medical Officer: This is a designated individual in the *Sponsor's Program* whose name is listed on the investigational new drug applications and who has the ultimate responsibility for overseeing all manufacturing activities conducted under these applications.

   3.2. Quality Assurance Administrator: This is a designated individual in the *Sponsor's Program* who is responsible for providing oversight and guidance to the *manufacturing site(s)* synthesizing radiopharmaceuticals under the *Sponsor's* Investigational New Drug applications.

   3.3. QA Auditor: This person or group of selected individuals from the *Sponsor's Program* is responsible for conducting audits of each of the *manufacturing site(s)* on a routine basis to ensure their compliance with all of the current standard operating procedures and to oversee the compliance for production of products according to the master production and the master batch records as they have been written.

   3.4 Manufacturing Site Principal Investigator: This is the designated principal investigator at the *manufacturing site* who has the ultimate responsibility for all of the production activities associated with the synthesis of the investigational radiopharmaceutical.

   3.5. Manufacturing Site Radiochemist/Pharmacist: This person or groups of individuals at the *manufacturing sites* will assist the principal investigator in the production of the investigational radiopharmaceutical agents.

3.6. Quality Control Units: Regardless of the size, scope, or complexity of the operation, the *manufacturing sites* are responsible for written policies describing how the Quality Control Units are staffed and managed at their individual sites.

3.7. Manufacturing Sites: *Manufacturing sites* should conduct verification testing of equipment and procedures used for the quality control testing of investigational PET radiopharmaceuticals upon initial installation or upon major repair. Equipment must also be checked on a routine schedule according to the site's written procedures and documented.

3.8. Note that on individual may perform more one of the functions.

4. DEFINITIONS

4.1. Radioactive Drug or Radiopharmaceutical: The term is defined in both 21 CFR 310.3 (n) and section 201 (g) (1) of the Federal Food, Drug, and Cosmetic Act, as a drug which exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons and includes any non-radioactive reagent kit or nuclide generator which is intended to be used in the preparation of any such substance but does not include drugs such as carbon-containing compounds or potassium-containing salts which contain trace quantities of naturally occurring radionuclides. The term "radioactive drug" includes a "radioactive biological product," as well.

4.2. Reagent Audit Trail: Materials and reagents used for the synthesis of radiopharmaceuticals should conform to established quality control specifications and tests. Procedures for the testing, storage, and use of these materials should be established and documented. In this context, a reagent is defined as any chemical used in the procedure leading to the final radiochemical product, whereas materials are defined as ancillary supplies (tubing, glassware, vials, etc.).

4.3. Master Production Record: The principal document describing how a product is manufactured. The master production record presents logical, chronological step-by-step instructions that document how the radiopharmaceutical is to be produced. Production can be discussed under headings, such as accelerator operation, radiochemical synthesis, purification steps, and formulation of the finished product. The entire production process should be pre-established and described in full detail, including the equipment and instrumentation that will be used in a specified and controlled manner as part of the approved production process.

4.4. Master Batch Production Record: The document that captures all control information, data, test results, and appropriate signatures. A master batch production record is generated for each batch of final product that is manufactured.

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5. REFERENCES

5.1. USP 28 ‹1015› Automated Radiochemical Synthesis Apparatus
5.2. USP 28 ‹821› Radioactivity
5.3. USP 28 ‹823› Radiopharmaceuticals for Positron Emission Tomography Compounding
5.4. GEN-Q003, "Receiving, Handling, Quarantine, and Release of Reagents & Supplies"
5.5. GEN-M001, "Writing & Revising Reagent & Supply Forms"
5.6. GEN-R009, "QC Testing, Review, & Final Release"
5.7. GEN-Q015, "Investigating Out of Specification QC Test Results"
5.8. GEN-Q110, "Filter Integrity Test by Bubble Point"
5.9. GEN-R006, "Product Labeling"
5.10. GEN-R005, "Drug Product Complaints"
5.11. GEN-R004, "Assigning Batch & Compounding Record Numbers to Production Runs"
5.12. GEN-M120, "Documentation of Manufacturing Variances"
5.13. GEN-R008, "Good Documentation Practices"
5.14. GEN-R502, "General Equipment Maintenance"
5.15. Draft Guidelines for PET Drug Products—Current Good Manufacturing Practice (CGMP)
5.16. Draft Guidelines for Radiopharmacy, EANM, Eur J Nucl Med Mol Imag (2003) 30:BP63-BP72 Vol. 30, No. 8, August 2003.
5.17. Good Manufacturing Practices, 21 CFR 211

6. POLICIES

6.1. Agreement State Programs & the Nuclear Regulatory Commission (NRC): The NRC has authority to enter into agreements with State governments, with the State assuming regulatory responsibility over the receipt, possession, use, disposal, storage, and transfer of by-product source and specified quantities of special nuclear material in that State. The State's program must be compatible with the NRC program and the State must have the technical capability to protect public health and safety.

6.2. In addition to Agreement States, other states may regulate the use of accelerator-produced or naturally-occurring radioactive materials which are not controlled by the NRC.

6.3. All firms that manufacture and/or produce reactor-produced radiopharmaceuticals are required to operate under a license issued by the NRC or a regulatory agency of an Agreement State. Under the provisions of these licenses, each manufacturer shall have an individual designated as a Radiation Safety Officer (RSO) or radiation protection specialist. In addition, those areas where radioactive drugs are produced and stored shall be posted with a placard or sign bearing the radiation symbol and describing the radiation and/or contamination levels, and the precautions to be taken while in those areas.

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7. PROCEDURES

7.1. QUALITY ASSURANCE OVERSIGHT

The function of this group is to provide oversight and guidance to the *manufacturing sites* synthesizing radiopharmaceuticals under the *Sponsor's* Investigational New Drug applications. This group will provide the following:

7.1.1. Oversight of production operations to ensure that radiopharmaceutical agents are being manufactured according to the current Master and Batch Production Records.

7.1.2. It is the responsibility of the Quality Assurance Administrator to oversee the control of the documentation process, such as the creation of new Standard Operating Procedures (SOPs), the revisions of current SOPs, and the archival of old ones.

7.1.3. Review of Completed Documentation

The QA Administrator will:

7.1.3.1. Review production records corresponding to the manufacture of product for accuracy and completeness.

7.1.3.2. Ensure that all out of specification (OOS) QC testing errors are investigated, documented, and corrective action is taken as applicable as per **GEN-Q015**, "Investigating Out of Specification QC Test Results," SOP.

7.1.3.3. Ensure that all manufacturing variances are documented as per **GEN-M120**, "Documentation of Manufacturing Variances" SOP, and either resolved or incorporated in the next revision of the Master Production and Master Batch Records, or QC SOPs as appropriate.

7.1.3.4. Provide guidance on any procedures affecting production, testing, and specifications.

7.1.3.5. Review drug complaints, investigate the nature of the complaints, send responses to the complaints, and file the necessary paperwork as applicable in the master file.

7.1.4. The QA Administrator should be notified immediately if any batch of final product fails to meet the sterility specifications. In addition the test results must be reported to all receiving facilities with appropriate recommendations and follow-ups.

7.1.5. Perform site audits on a regular basis. Records of these audits will be retained by the *Sponsor* in a master file.

7.2. GENERAL DOCUMENTATION PRACTICES

7.2.1. It is the responsibility of all personnel who utilize these SOPs, to initiate revisions of documentation when procedures are revised, equipment is changed, or omissions are noted. A revision may be initiated by notifying the Quality Assurance Administrator.

7.2.2. All documentation corresponding to production of radiopharmaceuticals, or manufacturing quality systems will be reviewed on a bi-annual basis to ensure that it is still current with the existing practices.

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7.2.3. Master Production and Master Batch Records

7.2.3.1. The Master and Batch Production Records unique to each radiopharmaceutical product will be written by the *Sponsor* and distributed to the assigned *manufacturing sites* for use in the production of the appropriate radiopharmaceutical(s).

7.2.3.2. Copies of the current Master Production Records should be available at all times in the production areas at the *manufacturing sites*.

7.2.3.3. For every batch of product manufactured, there should be a corresponding Batch Production Record with a unique Batch Number assigned as per **GEN-R004**, "Assigning Batch & Compounding Record Numbers to Batch Production Runs."

7.2.3.4. Copies of the superseded manufacturing and batch production records will be kept in a central master file for review by the *Sponsor*.

7.2.3.5. Completed batch production records corresponding to batches of final products will be retained in a master file at each *manufacturing site* for a period of at least 1 year(s) from the date of release. All records should be stored such that they are readily accessible for inspection and review.

7.2.4. Under cGMP regulations in 21 CFR Part 211, FDA normally requires second-person checks at various stages of the production as well as test verification. For production of PET agents staffing may only include one or two persons to accomplish all production and quality control functions.

7.2.4.1. In production areas where only one person is assigned to perform the production and quality control tasks, that person should check and recheck his or her own work. Self-checks should involve the repetitive confirmation of the operator's own action and should be documented.

7.2.4.2. At larger facilities that produce multiple drug products, the staffing level should be adequate to manage production and quality control functions. Personnel should be assigned to conduct second-person checks to verify each critical step in both the production and the quality control processes.

7.2.5. Control of Components, Materials, and Supplies

7.2.5.1. **GEN-M001** is the standard operating procedure that establishes the creation of written specification documents for identity, purity, and quality of components; the identity and quality of containers and closures, and other materials (e.g. purification devices, membrane filters) that come into contact with the final radiopharmaceutical; and the identity, purity, and quality of analytical supplies, sterility test media,

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endotoxin test reagents, and other supplies intended for use in radiopharmaceutical quality control procedures; and the appropriate storage of components, containers and closures, materials and supplies used for the compounding of radiopharmaceuticals.

7.2.5.1.1. All components, materials, supplies, or reagents used in the manufacture of radio-pharmaceuticals will be assigned a specification standard or "**SS**" that will be unique to each component, material, supply or reagent used in the process.

7.2.5.1.2. For each specification standard (**SS**), a document will be written outlining the specifications, manufacturer(s), storage requirements, and QC test requirements for that specific component/ material/ supply/ reagent.

7.2.5.2. **GEN-Q003** is the standard operating procedure that outlines the receiving, handling, distribution, and documentation of shipments of components, containers and closures, materials, and supplies used for the compounding of radiopharmaceuticals.

7.2.5.3. As per **GEN-Q003**, any component, material, and/or supply for use in the manufacturing process must be received, documented, assigned an internal tracking number, labeled as per **GEN-Q003**, and quarantined until a review can be completed. The review of a component, material, and/or supply's certification of analysis with the corresponding written internal specification ensures that it is of the appropriate identity, purity, and quality for the manufacturing process.

7.2.5.4. Each site should have written procedures for proper calibration, maintenance, and cleaning of manufacturing equipment. Refer to **GEN-R502**, "General Equipment Maintenance," SOP for the general requirements expected for all *manufacturing sites*. Each site should retain documentation corresponding to these activities in a master file for review purposes.

7.2.6. **<u>QC Test Sample Labels</u>** must contain a radioactive materials symbol with the words "Caution Radioactive Material," the batch number of the final product, the name of the radiopharmaceutical, the concentration in mCi/mL or Bq/mL & the time the activity was assayed, the test to be performed, date and time it was manufactured, initials of the

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radiopharmacist/chemist, and the expiration date and time as determined by appropriate stability testing.

7.2.7. **Final Product Labels** must contain a radioactive materials symbol with the words "Caution Radioactive Material," the designation of the laboratory in which the radiopharmaceutical was produced, the batch number of the product, the name of the radiopharmaceutical including the radionuclide, the concentration in mCi/mL or Bq/mL (as appropriate for your clinic) with the date and time it was assayed, the initials of the radiopharmacist/chemist, and the expiration date and time as determined by appropriate stability testing. Refer to **GEN-R006**, "Product Labeling." Additionally, each label shall have the statement. "Caution: New Drug-Limited by Federal (or United States) law to investigational use.

7.2.8. Training of Personnel

7.2.8.1. Personnel receive training both, through formal instruction at orientation and at more job-specific on-the-job training while performing their new duties. All training must be tracked and documented as required by the policies at the *manufacturing sites*.

7.2.8.2. Aseptic Area Operators are trained by supervisory personnel. Operators are evaluated through observation and microbial testing.

7.3. QUALITY CONTROL UNIT

The Quality Control Unit at each of the *manufacturing sites*:

7.3.1. Is required to perform quality control testing on batches of radiopharmaceuticals according to written procedures, and to document these results on the appropriate test forms.

7.3.2. Is required to have scientifically sound sampling procedures, as well as laboratory analytical test methodology that are sensitive, accurate, and reproducible.

7.3.3. Should use the appropriate equipment capable of producing valid results. There should be written procedures to ensure that the equipment is routinely calibrated, checked, and maintained, and that these activities are properly documented.

7.3.4. Will maintain a complete set of documentation of all testing performed related to the production of the radiopharmaceuticals to ensure compliance with established specifications and assays.

7.3.5. Will examine and approve or reject components, containers, closures, in-process materials, and labeling used in the production of radiopharmaceuticals to ensure that all of these meet their current specifications.

7.3.6. Will examine and approve or reject radiopharmaceuticals per the current specifications listed in the IND.

7.3.7. Will examine any procedure affecting production, testing, and specifications.

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7.3.8. Will investigate out-of-specification tests results and take the appropriate corrective action.

7.4. QUALITY CONTROL TESTING

7.4.1. The appropriate panel of tests is outlined in the corresponding IND for the radiopharmaceutical.

7.4.2. A description of the sample (including source, batch or lot number, date, and time the sample was received for testing) will be recorded.

7.4.3. Solutions used for conducting the quality control tests will be controlled by the use of established written procedures to compound and document their preparation. They will be appropriately labeled and assigned expiration dates accordingly.

7.4.4. Raw test data and any calculations performed must be documented and attached to the final product test form. This documentation becomes part of the batch record for that lot of material.

7.4.5. Any Out-of-Specification Results will be investigated and documented as per **GEN-Q015**, "Investigating Out of Specification QC Test Results." The OOS investigations are documented on **Form IOS-001**, "Investigating Out of Specification (OOS) QC Test Results" Form, and the unique investigation numbers are assigned using the **Form LOS-L**, "Out of Specification (OOS) Investigation Log," Form for tracking purposes.

7.5. FINAL PRODUCT CONTROLS AND ACCEPTANCE CRITERIA

7.5.1. Each batch of final product will be released as per its specific set of release criteria outlined in the corresponding investigational new drug application, (IND), for that radiopharmaceutical.

7.5.2. The radiopharmaceutical must meet its established acceptance criteria, except for sterility, prior to release. Sterility testing need not be completed before release, but it should be initiated within 24-48 hours from the time of manufacture as per **GEN-Q117**, "Sterility Test."

7.5.3. The release of the batch cannot occur until the appropriate testing is completed, the associated data and documentation are reviewed, and the release is authorized by the appropriate QC personnel.

7.5.4. If the batch of product does not meet all of the specifications it must be rejected, and the cause(s) of non-conformity must be investigated. This batch of material must then be segregated from all other batches of materials as appropriate.

7.5.5. Sterilization and Sterility Assurance

7.5.5.1. Microbiological Testing of the Laminar Flow Hood is performed periodically by the *manufacturing sites*, documented, and will be reviewed to ensure product sterility. Non-viable particle counting is performed less frequently, documented, and will be reviewed as well.

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7.5.5.2. "Bubble-point" testing is performed per **GEN-Q110**, "Filter Integrity Test By Bubble Point." The result of this test is attached to the corresponding batch production record.

7.6. FAILURE OF STERILITY RESULTS

7.6.1. For batches of final product that fail to meet the sterility specifications, the results of the tests will be immediately reported to all receiving facilities, with appropriate recommendations and follow-ups.

7.6.2. In addition the doctor who wrote the prescription for the radiopharmaceutical will be notified and this notification will be documented.

7.7. STABILITY TESTING

7.7.1. A proposed stability program may be written for each investigational agent according to the product storage conditions and the length of time the radiopharmaceutical will need to be stored.

7.7.2. The proposed stability program would include the following:

- appropriate testing to distinguish degradation products and impurities;
- be performed at the greatest radioactive concentration, and the whole batch volume in the intended container/closure will be stored at the appropriate conditions;
- at least three production runs of the final product for a time period equal to the labeled shelf life of the radiopharmaceutical.

7.8. FILING OF DRUG COMPLAINTS

7.8.1. Per **GEN-R005**, "Drug Product Complaints," all drug complaints should be reviewed by the quality assurance personnel to determine the possible cause of the complaint and logged onto **Form DPC-L**, "Drug Product Complaint Log," Form. The results of the investigation must be documented on **Form DCI-L**, "Drug Product Complaint Investigation Form."

7.8.2. Form DCI-L is a written record of the complaint that will be maintained in a file designated for radiopharmaceuticals as well as a copy of the complaint will be placed in the batch production record corresponding to the batch of final product.

7.8.3. The record will include the nature of the complaint received, the response to the complaint, the findings of the investigation and follow-up, or a reason why no investigation was conducted.

7.8.4. The radiopharmaceutical that is returned because of a complaint may not be reprocessed and must be destroyed.

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