Appendix IV Dispensing Process Control Standards

1. Medical institutions must have written dispensing process control procedures to ensure that all key process parameters are controlled and that any deviations from the procedures are justified.
2. Medical institutions must have dispensing process control records that must include the following information:
   - 2.1 The name and strength of the PET drug.
   - 2.2 The name and radioactivity of each active pharmaceutical ingredient and each added substance per batch or per unit of radioactivity or other measurement of the drug product, and a statement of the total radioactivity or other measurement of any dosage unit.
   - 2.3 A complete list of components designated by names and codes sufficiently specific to indicate any special quality characteristic.
   - 2.4 Identification of all major pieces of equipment used in dispensation.
   - 2.5 An accurate statement of the weight or measurement of each component, using the same weight system, and of the reasonable variations that are permitted in the amount of component necessary.
   - 2.6 A statement of action limits on radiochemical yield beyond which investigation and corrective action are required.
   - 2.7 Complete compounding and control instructions, sampling and testing procedures, specifications, special notations, and precautions to be followed.
   - 2.8 A description of the PET drug product containers, closures, and packaging materials, and a specimen or copy of each label of the PET drug product.

3. Medical institutions must create a unique batch production and control record of a PET drug each time. The batch production record must include the following information:

3.1 Name and strength of the PET drug.

3.2 Batch number.

3.3 Identification of major pieces of equipment used in production of the batch.

3.4 The name and radioactivity of each active pharmaceutical ingredient and each inactive ingredient per batch or per unit of radioactivity or other measurement of the drug product.

3.5 Names, Weights (or other measure of quantity) and identification codes of all components, drug product containers and closures that used in dispensing processes.

3.6 Approved dispensing process control records of each critical step.

3.7 Radiochemical yield.

3.8 Dates of dispensing steps and times of critical steps.

3.9 Testing results.

3.10 Labeling.

3.11 Signatures of persons performing or checking each significant step in the operation.

3.12 Investigation reports of unplanned deviations or unexpected results.

4. Unnecessary materials and labels should be removed from the work area and equipment before dispensation. The cleanliness and application of the work area and all equipment should be confirmed and recorded, and the record of these checks must be kept.

5. All equipment for preparing the PET drug product must be checked to ensure cleanliness.

6. The equipment that contacts the PET drug product should be removed from bacterial endotoxins, sterilized, and stored in a clean or sterile environment.

6.1 Medical institutions that self-sterilize such equipment should verify the sterility of the sterilization process and assembly components, and should periodically confirm their sterilization efficiency.

6.2 Sterile vials, injection needles, transfer sets, and membrane filters should be commercially available items.

7. Aseptic membrane filters and sterile containers should be assembled in the aseptic laminar airflow workstation, and operators should comply with the following provisions:

7.1 Operators should wear clean attire.

7.2 Operators should wear gloves before reaching into the aseptic laminar airflow workstation and disinfect them properly.

7.3 The protective envelope for covering and opening sterile items should be carried out in the aseptic laminar airflow workstation.

7.4 The sterile components should be placed in a sealed container before removing them from the aseptic laminar airflow workstation.

7.5 Product containers, filtering kits, membrane filter, and injection needles should be sterile, disposable, and only for single use.

7.6 The assembled kits should be maintained sterile when using the membrane filter to filter the PET drug product.

7.7 When any kit contacts a non-sterile surface, that is a risk of destroying sterility, the kit should be replaced.

7.8 The bottle rubber stopper should be wiped with 70% ethanol or isopropanol and other disinfectants before inserting into the product container, and evaporated naturally in the aseptic laminar airflow workstation.

8. The solution of the PET drug product for injection should be sterilized with a sterile membrane filter and filled into a sterile, pyrogen-free container; And the components, containers, closures and materials used in the aseptic filtration process should be aseptically operated in an aseptic environment.

9. Aseptic operations should be performed by qualified personnel who regularly pass the aseptic operation verification and in accordance with the following provisions:

9.1 Aseptic operation techniques should be validated by the simulation test for media fills which using microbial culture medium to replace the solution of PET drugs, and simulate the aseptic operation process of aseptic component connection and filtration; And the procedure is as follows:

9.1.1 After the simulation process for media fills is over, the product container should be shaken gently so that the filled medium touches all surfaces inside the container.

9.1.2 The container containing the culture medium should be placed at 30°C to 35°C, 20°C to 25°C or other suitable temperature for more than 14 days, and the microbial growth should be checked regularly during this period.

9.1.3 For the culture medium in the container without the growth of microbes, the test is considered as passed.

9.2 The initial simulation test of aseptic process should be performed on a daily basis, and the dispensing operation can only be started if it has passed three consecutive times. New operators should follow the same procedure before performing dispensing operations.

9.3 Operators should pass the simulation test at least once a year.

9.4 Each aseptic production line should pass the simulation test at least twice a year.

9.5 If there are obvious changes in the aseptic process (such as changes in personnel, components, or equipment) or there are signs that the product cannot be maintained sterile, the simulation test for media fills should be repeated.

10. Process controls must include control of in-process materials to ensure that the materials are tested, verified or necessary approvals are received, and the records should be kept.

11. The process and operational control for process verification are as follows:

11.1 It is necessary to confirm at least annually that the prescribed manufacturing process, facilities, equipment and computer programs can produce products that meet the predetermined specifications.

11.2 Those who have been approved and authorized can change the compounding program of the computer or related automation equipment; And the changes should be confirmed, recorded and kept.

11.2.1 The computer software used in the compounding should be the current valid version.

11.2.2 The software backup and written data used in the compounding should be stored in the master formula of the cyclotron of the medical institution. The replaced computer software, including the old version used before, should be stored separately from the master formula.

11.3 When the new compounding procedure or any changes in the manufacturing process, computer program, or component specifications may affect the identification, quality or purity of the product, three consecutive batches of process validation should be carried out before the change is approved.

11.4 The quality specifications confirmed by the manufacturing

process for the PET drug product that is included in the Chinese Pharmacopoeia, the United States Pharmacopoeia or the European Pharmacopoeia should be complied with the standards of these compendial test procedures.

11.5 When the initial sub-batch in a series (for PET drug products with a half-life of less than 25 minutes radionuclides) is tested, the PET drug producer must demonstrate that the process for producing the PET drug is capable of producing a drug product that meets the predetermined acceptance criteria. Process verification activities and results must be documented. Documentation must include the date and signature of the individuals performing the verification, the monitoring and control methods and data, and the major equipment qualified to ensure that its compounding procedures, equipment and facilities meet established standards.