Radiopharmaceutical Quality Control

USP “797” Standards for the Radiopharmacy

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SNMTS Approved

MIVWIQII: PET Radiopharmacy Quality Control
45 Hr PET Registry Review Course
Reference Number: 028626
1.5 CEH’s
Program Objectives

Discuss the background of the USP
Review personnel cleansing and gowning
Discuss the responsibilities of compounding personnel
Review the Risk Level Classifications
Verifying the accuracy and sterilization technique
Discuss personnel training and assessment
Review quality control equipment
Discuss the Storage and Beyond Use dating
• United States Pharmacopeia (USP)
  – Non-governmental non-profit organization
  – Primary activities are creation of standards, patient safety, healthcare information, and verification of products
    • Quality and consistency of medicines
      – Prescription
      – Non-prescription
      – Dietary supplements
      – Veterinary drugs
      – Healthcare products
    • Safe and proper use of medications
  – USP standards are developed by a unique process of public involvement
USP Legal and Regulatory Basis

- **Food and Drugs Act – 1906**
  - US Pharmacopeia (USP/NF) became the official standard for drugs in the United States

- **Federal Food, Drug and Cosmetic Act – 1938**
  - USP/NF official compendia of drug standards
  - Food and Drug Administration (FDA) responsible for enforcement of the act
  - FDA may enforce required standards in USP/NF
USP Legal and Regulatory Basis (cont.)

- Each general chapter of the USP/NF is assigned a number which appears in brackets

- Chapter <1> to <999> are required
  - Pharmacies are subject to inspection for compliance with required standards by:
    - Boards of Pharmacy
    - FDA
    - Joint Commission on Accreditation of Healthcare Organizations (JCAHO)
    - Includes Chapter <797>

- Chapter <1000> to <1999> are informational
Goal of Chapter <797>

- Goal of USP Chapter <797> is to prevent potential patient harm or death that could result from:
  - Microbial contamination
  - Excessive bacterial endotoxins
  - Large content errors in the strength of correct ingredients
  - Incorrect ingredients
Definition of Compounded Sterile Products (CSP) – USP27 <797>

- Preparations prepared according to the manufacturer’s labeled instructions and other manipulations that expose contents to potential contamination

- Preparations containing nonsterile ingredients or employ nonsterile components or devices that must be sterilized before administration

- Biologics, diagnostics, drugs, nutrients, and radiopharmaceuticals that possess either of the above two characteristics
Scope of USP <797> Multidisciplinary

Chapter USP <797> applies to pharmacists, physicians, nurses, and allied health team members.
• Personnel cleansing and gowning
• Responsibilities of compounding personnel
• Risk level classification of Compounded Sterile Products (CSP) and quality assurance
• Verification of accuracy and sterilization of CSP
• Personnel training and assessment
• Environmental quality and control
• Equipment
• Storage and beyond-use dating
• Hand Washing
  – Wash hands, nails and arms up to the elbow with soap and water
  – Wash for at least 15 seconds (Sing alphabet song)
  – Use a disposable scrub brush to clean nails and between fingers
  – Dry hands with non-shedding towel
  – Turn off faucet with towel or use foot pedals
After washing hands, put on non-shedding uniform components in this order:

- Knee-length coats or coveralls
- Hair cover
- Shoe covers
- Protective gloves
- Face mask when in hood
• Hair Covers
  – Must cover all hair
  – Beards and long sideburns require use of beard cover

• Gloves
  – Powder free
  – Clean new gloves with 70% isopropyl alcohol before use
  – Avoid touching non-sterile surfaces
  – Intermittently sanitize gloves with 70% isopropyl alcohol
• Every time you leave the buffer area you must **remove** and **discard** your:
  – Hair cover
  – Gloves
  – Face mask

• **Must remove lab coat when leaving buffer area**
  – May hang coat inside out
  – Must discard coat at the end of each shift
• Face mask must be worn while in hood
  – Minimizes airborne contaminants while talking, sneezing and coughing
  – Must cover mouth and nose completely
• Personnel cleansing and gowning
• **Responsibilities of compounding personnel**
• Risk level classification of Compounded Sterile Products (CSP) and quality assurance
• Verification of accuracy and sterilization of CSP
• Personnel training and assessment
• Environmental quality and control
• Equipment
• Storage and beyond-use dating
• Manipulate sterile products aseptically
• Ensure products are accurately
  – Identified
  – Measured
  – Diluted
  – Mixed
• Maintain appropriate cleanliness conditions

• Ensure products are correctly
  – Purified
  – Sterilized
  – Packaged
  – Sealed
  – Labeled
  – Stored
  – Dispensed
  – Distributed
• Open or partially used packages for subsequent use are:
  – Properly stored
  – Clearly labeled with date and time opened or date and time of expiration
• Labels on products must list names, amounts added and concentrations of all ingredients

• Before dispensing and administration, products are visually inspected for clarity

• Beyond-use dates are assigned based on direct testing or extrapolation from reliable literature and other documentation
Low-Risk Level Characteristics

- **Low-Risk Conditions**
  - Products compounded with aseptic manipulations entirely within ISO class 5 quality air using only sterile ingredients, products, components or devices
  - Involves only transfer, measuring, and mixing manipulations with closed or sealed packaging systems performed promptly and attentively
  - Manipulations limited to aseptically opening ampules, penetrating sterile stoppers on vials with sterile needles and syringes, and transferring sterile liquids in sterile syringes to other sterile products
Low-Risk Level Characteristics (cont.)

- **Examples of Low-Risk Compounding**
  - Single transfers of sterile dosage forms from ampules, bottles, bags, and vials using sterile syringes with sterile needles, and other sterile containers. The contents of ampules requires sterile filtration to remove glass particles
  - Manually measuring and mixing no more than three manufactured products to compound drug admixtures
  - Tobramycin piggyback
  - Morphine drip
Low-Risk Level Characteristics (cont.)

• Quality Assurance
  – Routine disinfection of the direct compounding environment to minimize microbial surface contamination
  – Visual conformation that personnel are properly garbed with hair covers, gloves, masks, etc.
  – Review of all products to ensure correct identity and amounts of ingredients were compounded
  – Visual inspection of products to ensure the absence of particulates in solutions, the absence leakage from vials or bags, accuracy of labeling
Medium-Risk Level Characteristics

- Medium-Risk Conditions include **all** low-risk conditions in addition to one or more of the following:
  
  - Multiple individual or small doses of sterile products are combined or pooled to prepare a product that will be administered to multiple patients or the same patient on multiple occasions
  
  - Compounding includes complex aseptic manipulations other than single volume transfer
  
  - Compounding requires unusually long duration to complete dilution or homogenous mixing
  
  - The product does not contain bacteriostatic substances and is administered over several days (e.g. external or implanted pump)
Medium-Risk Level Characteristics (cont.)

- Examples Medium-Risk Compounding
  - Compounding of total parenteral nutrition using manual or automated devices
  - Filling of reservoirs of injection and infusion devices
    - with multiple sterile products
    - administered over several days at ambient temperatures (implanted pumps)
  - Transfer of volumes from multiple ampules or vials into a single, final sterile container or product (terbutaline drip)
  - Hydromorphone IVPCA batches using commercial sterile ingredients
Medium-Risk Level Characteristics (cont.)

- Quality Assurance
  - Routine disinfection of the direct compounding environment to minimize microbial surface contamination
  - Visual conformation that personnel are properly garbed with hair covers, gloves, masks, etc.
  - Review of all products to ensure correct identity and amounts of ingredients were compounded
  - Visual inspection of products to ensure the absence of particulates in solutions, the absence leakage from vials or bags, accuracy of labeling
High-Risk Level Characteristics

- High-Risk Conditions include **all** low-risk and medium-risk conditions in addition to one or more of the following
  - Non-sterile ingredients are incorporated or a non-sterile device is employed before terminal sterilization
  - Sterile ingredients, components, devices, and mixtures are exposed to air quality inferior to ISO class 5
  - Non-sterile preparations are stored greater than 6 hours before being sterilized
High-Risk Level Characteristics (cont.)

- Examples of High-Risk Compounding
  - Dissolving non-sterile bulk drug and nutrient powders to make solutions, which will be terminally sterilized
  - Exposure of sterile ingredients to air less than ISO class 5 (e.g. nursing preparation on the ward)
  - Measuring or mixing of sterile ingredients in non-sterile devices before sterilization is performed
High-Risk Level Characteristics (cont.)

- Quality Assurance
  - Routine disinfection of the direct compounding environment to minimize microbial surface contamination
  - Visual conformation that personnel are properly garbed with hair covers, gloves, masks, etc.
  - Review of all products to ensure correct identity and amounts of ingredients were compounded
  - Visual inspection of products to ensure the absence of particulates in solutions, the absence leakage from vials or bags, accuracy of labeling
Media-Fill Testing

- **Low and Medium Risk Levels**
  - Personnel authorized to compound low or medium risk products are required to perform media-fill testing **annually**
  - Test must simulate most challenging and stressful conditions during compounding of low or medium risk products respectively

- **High-Risk Level**
  - Personnel authorized to compound high-risk products are required to perform media-fill testing **semi-annually**
  - Test must simulate most challenging and stressful conditions during compounding of high-risk products
• Personnel cleansing and gowning
• Responsibilities of compounding personnel
• Risk level classification of Compounded Sterile Products (CSP) and quality assurance
• Verification of accuracy and sterilization of CSP
• Personnel training and assessment
• Environmental quality and control
• Equipment
• Storage and beyond-use dating
• **Physical Inspection**
  - Finished products to be individually inspected for
    • Particulates
    • Foreign matter
    • Container-closure integrity
    • Other apparent visual defects
  - Products not immediately distributed must be inspected before leaving the storage area
• Compounding Accuracy Checks
  – Written procedures for double-checking compounding accuracy must be followed
  – Double check should include label accuracy and accuracy of the addition of all products or ingredients
  – Used containers and syringes should be quarantined with the final product until double check is performed
  – Double check should be performed by person other than the compounder
• Sterilization and Bacterial Endotoxin Testing
  – Required for high-risk level products that involve nonsterile products or devices
  – Product must be tested according to USP Chapter <85> Bacterial Endotoxins Test
  – Sterilization Methods
    • Dry Heat
      – 250°C for two hours
    • Steam (autoclave)
      – 121°C at 15 pounds per square inch (p.s.i.) for 20 to 60 minutes
    • Filtration
      – 0.2 micron filter certified to retain $10^7$ Brevundimonas diminuta per cm$^2$
    • Must verify sterilization procedures
      – Required to prove it
      – Accomplish with media fill testing
• Personnel cleansing and gowning
• Responsibilities of compounding personnel
• Risk level classification of Compounded Sterile Products (CSP) and quality assurance
• Verification of accuracy and sterilization of CSP
• Personnel training and assessment
• Environmental quality and control
• Equipment
• Storage and beyond-use dating
• Personnel who prepare compounded sterile products or parenteral preparations must be provided with appropriate training in the theoretical principals and practical skills of aseptic manipulations.

• Assessment of knowledge and skills
  – **Annually** for personnel preparing low and medium-risk level products
  – **Semi-annually** for personnel preparing high-risk level products
• Assessment
  – Written tests
  – Media-fill challenge testing
  – Failure of assessment requires re-instruction and re-evaluation before being allowed to compound sterile products

• Media-fill challenge testing
  – Sterile bacterial culture medium transferred via a variety of aseptic manipulations
  – Test should represent the most challenging products made for a particular risk level
  – Products are monitored for microbial growth, indicated by visual turbidity, for 14 days
• Personnel cleansing and gowning
• Responsibilities of compounding personnel
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• **Critical Site**
  - Any opening providing a direct pathway between a sterile product and the environment or any surface coming into direct contact with the product and the environment
  - Must protect these sites from environmental contamination

• **Air Quality**
  - ISO Class 5 (Class 100) required in critical area (area where sterile products are directly exposed, e.g. hood)
  - ISO Class 8 (Class 100,000) required for buffer area or clean room
  - Minimize air currents from open doors, personnel traffic and ventilation ducts
  - Air conditioning and humidity control required
• Cleaning and sanitizing workspaces
  – Standard operating procedures are required

• Environmental monitoring
  – Air quality inspections (every 6 months)
  – Certification of hoods and barrier isolators (every 6 months)
  – Evaluation of airborne microorganisms
    • Monthly for low and medium risk-level compounding areas
    • Weekly for high risk-level compounding areas
• Personnel cleansing and gowning
• Responsibilities of compounding personnel
• Risk level classification of Compounded Sterile Products (CSP) and quality assurance
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• Personnel training and assessment
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• Equipment
• Storage and beyond-use dating
• Personnel are to be trained to operate any piece of equipment or apparatus they may use to prepare compounded sterile products
• Equipment calibration documentation
• Annual and routine maintenance documentation
• Monitoring for proper function documentation
• Procedures for use
• Calibration and maintenance reports to be kept on file
• Personnel cleansing and gowning
• Responsibilities of compounding personnel
• Risk level classification of Compounded Sterile Products (CSP) and quality assurance
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• Storage and beyond-use dating
Storage and Beyond-Use Dating

In the absence of sterility testing, storage periods (before administration) shall not exceed the following based on sterility:

<table>
<thead>
<tr>
<th></th>
<th>Low-risk</th>
<th>Medium-risk</th>
<th>High-risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Room Temp &gt;8°C</td>
<td>≤48 hours</td>
<td>≤30 hours</td>
<td>≤24 hours</td>
</tr>
<tr>
<td>Refrigerated 2°C to 8°C</td>
<td>≤14 days</td>
<td>≤7 days</td>
<td>≤3 days</td>
</tr>
<tr>
<td>Freezer ≤20°C</td>
<td>≤45 days</td>
<td>≤45 days</td>
<td>≤45 days</td>
</tr>
</tbody>
</table>
• Use stABility dating only if shorter than stERility beyond-use dating recommendations
  – Low-risk level product “ABC” in refrigerator would receive a beyond-use date of \( \leq 7 \) days based on stERility
  – If the stABility of product “ABC” is 24 hours, then product should be labeled with beyond-use date of \( \leq 24 \) hours

• Beyond-use dating can be extended if direct sterility testing is performed
• Single dose or single use vials shall be discarded within:
  – 24 hours if stored at room temperature
  – 72 hours if stored in the refrigerator
• Multi-dose vials shall be discarded within 28 days
• Beyond-use dating can be extended if direct sterility testing is performed
Summary

- USP<797> is an important patient safety initiative
- Adoption of the standards will require personal motivation and teamwork
- For more information on USP<797> visit http://www.ashp.org/SterileCpd/
- USP<797> is under continual revisions. Please obtain a current copy of the chapter for the most current information.