



The University of New Mexico Health Sciences Center
COLLEGE OF PHARMACY



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***USP Chapter <797>
Pharmaceutical Compounding —Sterile Preparations
Potential Impact on Handling Radiopharmaceuticals***

Continuing Education for Nuclear Pharmacists and
Nuclear Medicine Professionals

By

James F. Cooper, Pharm.D.
CGMP Consultant

And

Neil A. Petry, M.S., BCNP
Director, Radiopharmacy Services
Duke University Medical Center



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UNM College of Pharmacy

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USP CHAPTER <797> PHARMACEUTICAL COMPOUNDING — STERILE PREPARATIONS

Potential Impact on Handling Radiopharmaceuticals

STATEMENT OF OBJECTIVES

Upon completion of this course the participant will be able to discuss the general concepts and principles associated with the provision of compounded sterile preparations (CSPs) as specified by USP Chapter <797>, and apply them in a variety of nuclear pharmacy practice settings.

Specifically, the participant should be able to:

1. Identify the key acronyms and state the definition of key terms associated with *USP <797>*.
2. Describe both the general responsibilities of compounding personnel and those specific to the practice of nuclear pharmacy.
3. Identify the specific categories of compounded sterile product microbial contamination in terms of risk levels.
4. Compare and contrast the specific requirements associated with these risk level categories.
5. Discuss the procedures and disinfectants that are needed to control of surface contamination.
6. Discuss the procedures, cleanroom etiquette and equipment that are essential for control of airborne organisms.
7. Create a floorplan illustrating the critical design features needed for *USP <797>* compliance.
8. Discuss the requirements associated with the training of personnel and assessment of their aseptic manipulation skills.
9. Discuss the general requirements for personnel cleansing and garbing, and suggest how these may apply to radiopharmaceutical compounding.
10. Provide a rationale for written procedures that guide and motivate personnel.
11. Demonstrate an ability to assess and verify the adequacy of the environmental monitoring of aseptic compounding areas.
12. Describe how to: a.) maintain the sterility of dispensed radiopharmaceutical CSPs, and b.) achieve sterility of radiopharmaceuticals compounded from non-sterile components.
13. Create a floor plan illustrating the key design features necessary to assure compliance.
14. Understand the consequences of inadequate sterile compounding practices.
15. Understand the complex legal standing and implications of *USP Chapter <797>* as they apply to healthcare organizations, hospitals, pharmacists and other practitioners.

COURSE OUTLINE

I.	Preface	7
II.	INTRODUCTION	8
	A. Justification for Sterile Compounding Practice Guidelines and Standards	8
	B. General Chapter <797> and the USP Revision Process	10
III.	SCOPE OF USP CHAPTER FOR COMPOUNDING STERILE PREPARATIONS	11
	C. Overview: Contamination Control for Parenterals	11
	D. Applicability of Compendial Guides to Sterile Radiopharmaceuticals	11
	E. Microbial Risk Levels for CSPs used in Nuclear Pharmacy Practice	12
IV.	CONTROL OF SURFACE CONTAMINATION	13
	F. Cleaning and Disinfection	14
	G. Critical Sites: Syringes, Needles and Vials	16
	H. Decontamination of Reusable Shields	18
V.	CONTROL OF AIRBORNE CONTAMINATION	19
	I. Air Quality Classification	19
	J. Primary Engineering Controls	19
	K. Environmental Monitoring (EM)	20
VI.	PERSONNEL CLEANSING AND GARBING	21
	L. Hand Hygiene	21
	M. Garbing	23
VII.	DESIGN OF A NUCLEAR PHARMACY	23
VIII.	PERSONNEL MANAGEMENT	28
IX.	PERSONNEL MANAGEMENT	28
	N. Policies and Procedures	28
	O. Personnel Training and Evaluation in Aseptic Manipulation Skills	29
X.	ACHIEVING STERILITY OF COMPOUNDED RADIOPHARMACEUTICALS	30
	P. Sterilization	30
	Q. Membrane Integrity Test	31
	R. Sterility Test Methods	32
	S. Bacterial Endotoxins Test (BET) Methods	33
XI.	ENFORCEABILITY AND RECOGNITION	34

T. Drug Enforcement Agencies.....	34
U. Joint Commission on Accreditation of Healthcare Organizations (JCAHO).....	35
XII. SUGGESTED READING:	36
XIII. SUMMARY AND CONCLUSIONS	36
XIV. REFERENCES	37
XV. QUESTIONS	40

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PREFACE

The objective of *USP Chapter <797>* is to “describe conditions and practices to prevent harm, including death, to patients that could result from the following: 1) microbial contamination (nonsterility), 2) excessive bacterial endotoxins, 3) variability in the intended strength of correct ingredients that exceeds either monograph limits for official articles or 10% for nonofficial articles, 4) unintended chemical and physical contaminants and 5) incorrect types and qualities of ingredients in Compounded Sterile Preparations (CSPs).” (From General Chapter <797> Proposed Revisions accessed at <http://www.usp.org/USPNF/pf/generalChapter797.html> on August 20, 2007) This site also offers the following update on the revision process:

“The Sterile Compounding Expert Committee is carefully reviewing and considering all comments received on or before the August 15, 2006 public commentary deadline. There are approximately 2500 pages of comments from over 300 participants including hospitals, professional associations, vendors, stakeholders, individual practitioners including pharmacists, nurses and physicians, etc.

Due to the volume and criticality of these comments, it is not known when the review of comments to the proposed revisions will be completed, and the proposed revisions finalized. USP will post the Expert Committee's responses along with a summary of comments on the website in this location. Please continue to check our website for any additional updates.”

The Board of Pharmacy in each State must grapple with the changing environment for regulating sterile compounding. Predictably, they are taking different approaches to the implementation of the requirements set forth in *USP Chapter <797>*. Because of the many differing approaches the States are taking with regard to recognizing, implementing and enforcing *USP Chapter <797>* compounding standards, pharmacists should contact their Board of Pharmacy directly to obtain the specific language appearing in applicable state laws and regulations.

INTRODUCTION

Justification for Sterile Compounding Practice Guidelines and Standards

The profession of pharmacy has provided the necessary services related to the provision of compounded sterile preparations (CSPs) for over four decades. The first reports of centralized pharmacy intravenous (IV) admixture service were published in the late 1960's and early 1970's.^{1,2} Over time, as the provision of service related to the preparation of CSPs has expanded, the profession has invested significant effort to develop multiple guidelines and standards.³⁻⁶ The existence of these guidelines and standards clearly demonstrate the profession's commitment to the delivery of accurate, safe, and sterile CSPs to patients. Although sterile product preparation has historically been an area of inconsistent compliance within pharmacy practice, a recent survey indicates that the nation's first enforceable CSP guideline is having a positive influence on quality assurance practices.⁷

In the early 1990s, serious medication errors, aseptic complications, and total parenteral nutrition (TPN) precipitation problems occurred. Some of these incidents resulted in patient injury and death, gaining the attention of the Food and Drug Administration (FDA).⁸⁻¹³ Unfortunately, even though the FDA enhanced its regulatory enforcement and the profession of pharmacy further increased its efforts to raise the compounding practice standards, the occurrence of similar safety incidents continued into the new millennium. In 2002, there were cases in Walnut Creek, CA, involving the compounding of injectable medications which had tragic outcomes. In these cases, significant compounding errors, including insufficient steam sterilization, led to contamination with bacteria from inadequate aseptic technique during the preparation of injectable betamethasone. The compounded preparation was subsequently used for spinal injections, resulting in three deaths along with over thirty hospital admissions.^{14, 15}

Again in 2002, there were three cases of fungal meningitis and one death in North Carolina associated with the use of a contaminated injectable methylprednisolone preparation compounded and distributed by a Spartanburg, S.C. urgent care pharmacy.¹⁶ In 2003, the Centers for Disease Control and Prevention (CDC) reported their findings regarding a case where *Enterobacter cloacae* bloodstream infections in pediatric patients were traced to a hospital pharmacy.¹⁷ In this case, the CDC's analysis of patients' *E. cloacae* isolates identified four different pulsed-field gel electrophoresis (PFGE) patterns, suggesting environmental rather than point-source contamination. The hospital pharmacy routinely kept ranitidine multidose vials connected to an automatic compounding machine for up to 48 hours at room temperature after the first dose was drawn, contrary to manufacturer recommendations.

In addition, the preparation of ranitidine infusions was not conducted in accordance with recommendations for medium-risk level sterile intravenous products. It was concluded that the use of contaminated ranitidine multidose vials was the most likely cause of this outbreak. However, a combination of several other factors such as inadequate hand-washing techniques, presence of *E. cloacae* in the environment, noncompliance with guidelines for the preparation of sterile infusions and medications, and a susceptible patient population may have contributed to the infections.

In December of 2004, a contamination incident occurred in a Maryland nuclear pharmacy that caused an outbreak of hepatitis C among at least 12 patients who received doses of a cardiac imaging agent from a vial prepared at the facility.¹⁸ Although the root cause of incident was not conclusively determined, a plausible explanation is that a saline diluent used in cell labeling was inadvertently contaminated with sera from a hepatitis patient and then transferred to the area where Tc 99m kits are made. The consequences of this incident were devastating; the death of one elderly patient may have been related to hepatitis C, at least 12 patients were infected with a chronic, poorly treatable blood-borne disease, and there was loss of livelihood and commercial interest upon permanent closure of the facility.

Unfortunately, articles focused on the public safety concerns for compounded drug preparations appear frequently in both the main stream and alternative media. For example, a significant article published in the February 27, 2004 edition of *The Wall Street Journal* reviewed the stirring debate over the relative importance of “compounders” meeting special medication needs versus the need to close the regulatory gap to assure public safety.¹⁹ In 2005, it was still very obvious that drug safety was at forefront of the public awareness as indicated in a article published on March 23, 2005 at USATODAY.com questioning whether pharmacies are skirting federal law by mass-producing drugs without proper FDA oversight, sometimes making contaminated, ineffective or too-potent products.²⁰ Pharmacists should definitely find these articles and the associated issues extremely alarming and must rapidly come to the only possible rational conclusion, the profession of pharmacy and each individual pharmacist must do the right thing and do it much better than ever before. As pharmacists we must choose to be aggressively proactive in self-regulating pharmacy compounding practice at the state level or we can continue to passively ignore the public demand for safe compounded preparations and, in the process, run the risk of abdicating our compounding privileges to federal control. Compliance with professional standards is the only guarantee against federal regulation.

General Chapter <797> and the USP Revision Process

The U.S. Pharmacopeia's (USP) *General Chapter <797> Pharmaceutical Compounding – Sterile Preparations (Chapter <797>)* sets out a framework of practice standards to help ensure that CSPs are of high quality.⁷ When these standards are properly implemented they help prevent contamination of patient preparations..

Chapter <797> first became official on January 1, 2004, in USP 27 following its development out of *Chapter (1206) Sterile Products for Home Use*, which first became official when published in 1995 in USP 23. By convention, General Chapters numbered above 1000 are not official but intended for informational purposes only, therefore, the provisions in *Chapter (1206)* were never uniformly accepted nor implemented by compounders of sterile products. The USP Sterile Compounding Committee (SCC) of experts changed this chapter significantly and made it enforceable as *General Chapter <797>* in response to the growing concerns about the overall quality of compounded sterile preparations.

As expected, USP began to receive many substantive comments about the real and perceived deficiencies in *USP Chapter <797>* shortly after it became official and enforceable in 2004. Understanding the weightiness of the concerns expressed, the SCC undertook further revision of *Chapter <797>* in a timely, responsive manner. The USP proposed significant revisions to the Chapter in the *Pharmacopeial Forum 32(3)*, May-June 2006, the USP's journal of standard development and official compendia revision. USP also provided a Guidebook that contained easy-to-read versions of the proposed revisions.²¹ The Guidebook documented the results of the SCC's efforts to revise *Chapter <797>* and thereby incorporate needed change into the official standards for sterile compounding.²¹ USP used the Guidebook along with other activities, such as online web based seminars, to ensure that these proposed revisions were effectively communicated to practitioners and other stakeholders. The public review and comment component of a standard-setting process is essential, therefore, effective revision of *Chapter <797>* will continue to progress through strong and proactive participation of all compounding professionals, health care organizations and other stakeholders.

Pharmacists are directed to their State Board of Pharmacy regulations for the most current requirements for sterile compounding.

SCOPE OF USP CHAPTER FOR COMPOUNDING STERILE PREPARATIONS

Overview: Contamination Control for Parenterals

Pioneering microbiologists in the 19th century proved that invisible bacteria and their toxins were responsible for much human disease and suffering. Discoveries in the 20th century led to the development of drugs and infusion solutions to combat disease as well as methods to make injectables safe. The term *parenteral* is derived from the Greek “para” (beyond) and “enteral” (gut) because it bypasses the digestive system. This route of administration is so efficient that it necessitates a level of purity that approaches the absolute. Bacteria or viruses injected into the circulatory system evade all but the final mechanism of defense, the immune system; a contaminated drug or diagnostic agent intended for healing could instead bring infection, fever, shock or death. Williams²² wrote that man’s war against microbes is never ultimately won.

“They are deeply entrenched in the air, water, and soil. The body itself is occupied: 1% or more of the human genome consists of retroviral sequences and microbes on and in the body outnumber the cells that compose the body by 10-fold. Microbes are legion; ubiquitous, unmerciful and untiring. On a personal basis, those occupying us now, or their offspring, will decompose us when we die. They can be eradicated only in small places and for a short time.”

The complete eradication of microbes requires elimination of viable particulates (e.g., *Bacillus cereus* endospores on dust particles) in **AIR** exposed to an aseptic process and destruction of microbes and their pyrogenic toxins from the components on **SURFACES** in immediate contact with the drug product, known as “critical sites.” Airborne contamination is controlled by a properly certified, maintained and sanitized laminar air flow workbench (LAFW) and other environmental controls. *USP Chapter <797>* describes the essentials of air quality, aseptic technique and cleanroom behavior. Surface contamination is generally managed, for example, by proper use of 70% IPA (isopropyl alcohol) that rapidly destroys vegetative bacteria or by use of agents that also destroy bacterial endospores and yeast spores.

Applicability of Compendial Guides to Sterile Radiopharmaceuticals

The *USP Chapter <797>* specifies that sterile compounding pertains to all pre-administration manipulations of compounded sterile preparations (CSPs), including compounding, storage, and transport, but not their administration to patients. Sterile compounding requires **maintenance** of sterility when compounding exclusively with sterile ingredients and components, and the **achievement**

of sterility when compounding with non-sterile ingredients or components. *Chapter <797>* of the *USP* assigned three risk levels for preparing injectables that require more strict controls as microbial risk level increases. This CE unit focuses on aseptic processing of radiopharmaceuticals. Topics such as quality assurance testing and verification of compounding accuracy are not covered here because these are practices that are particularly well controlled in nuclear pharmacy and are the subject of other CE units.

Microbial Risk Levels for CSPs used in Nuclear Pharmacy Practice

Recent revision activity clarified the microbial risk level assigned to radiopharmaceutical CSPs and addressed specific concerns.²¹ Low-risk compounding applies to radiopharmaceutical CSPs that are compounded according to the manufacturer’s directions and meet quality assurance requirements, such as shelf life, procedures and environmental controls. Routine preparation of Tc 99m injectables, according to the supplier’s directions, exemplifies low-risk level activity, provided they are prepared by qualified personnel in an ISO Class 5 (formerly Class 100) laminar-air flow workbench (LAFW) or compounding aseptic isolator (CAI) that is located in an ISO Class 8 (formerly Class 100,000) buffer area. Additional requirements relative to Tc 99m drugs are that radiopharmaceutical dosage units have a volume of 15 mL or less and expiration times of 18 hours or shorter. Table 1 from *USP Chapter <797>* is included here for reference.

Table 1. International Organization of Standardization (ISO) Classification of Particulate Matter in Room Air [Limits are in particles 0.5 µm and larger per cubic meter (current ISO) and cubic feet (former Federal Standard No. 209E, FS 209E).]^{*}

Class Name		Particle Count	
ISO Class	U.S. FS 209E	ISO, m ³	FS 209E, ft. ³
3	Class 1	35.2	1
4	Class 10	352	10
5	Class 100	3520	100
6	Class 1000	35,200	1000
7	Class 10,000	352,000	10,000
8	Class 100,000	3,520,000	100,000

^{*} Adapted from former Federal Standard No. 209E, General Services Administration, Washington, DC, 20407 (September 11, 1992) and ISO 4644-1:1999, Cleanrooms and associated controlled environments—Part 1: Classification of air cleanliness. For example, 3520 particles of 0.5 µm per m³ or larger (ISO Class 5) is equivalent to 100 particles per ft³ (Class 100) (1 m³ = 35.2 ft³).

Low-Risk Level also applies to sterile, cyclotron-produced drugs that contain preservatives and bear expiration time of 72 hours or less. Generator systems for Tc 99m must be eluted according to applicable regulations and use instruction, and the elution process must be done in an ISO Class 8 environment. Compliance with these requirements also means that the specified preservative cover for the elution needles must be in place during the shelf life of a generator. Preparation of any pharmacological intervention agent from commercial products is also low risk activity. While radio-labeling of blood cells has a medium risk, it is also a biohazard. As such, it must be isolated from other nuclear-pharmacy functions, and must be guided by a specific set of procedures that avoid cross-contamination. The preparation of PET drugs, under *USP Chapter <823>*, and other radiotracers from non-sterile components is considered high-risk level and requires stringent controls and microbiological testing to assure sterility and freedom from pyrogens. Health care professionals are exempted from environmental requirements for “immediate use” compounding, which may include Rb 82 generator elution, but aseptic technique is an expected performance behavior. Immediate use is not an exemption intended for radiopharmaceutical compounding outside the hospital setting. The following table exemplifies risk levels for representative sterile CSPs in the opinion of the authors.

Table 2

Microbial Risk Levels for Representative CSPs in Nuclear Pharmacy Practice			
Agent	Risk	Agent	Risk
⁶⁷ Ga-gallium citrate	Low	¹³¹ I-tositumomab	Low
¹¹¹ In-pentetate (DTPA)	Low	★ ^{99m} Tc-labelled cells	Med
¹³¹ I-iobenguane (MIBG)	Low	★ ¹¹¹ In-labelled cells	Med
¹²³ I-iobenguane (MIBG)	High	²⁰¹ Tl-thallous chloride	Low
⁸² Rb generator eluate	Immediate	Interventional CSPs	Low

★ Note that while the labeling of patient blood products must be done under sterile/aseptic conditions, the blood itself is not sterile. Patient blood and blood products are considered a biohazardous risk to operators. During the labeling procedure sterile controls must be carefully balanced against control of biohazards. The manipulations of blood products must be clearly separated from “routine” CSP activities in such a manner that cross-contamination cannot occur.

C CONTROL OF SURFACE CONTAMINATION

Requirements for aseptic compounding necessitate impeccable surface cleaning and disinfection in efforts to minimize the opportunity for bacterial growth and contamination. Pharmacists must develop written procedures that specify the frequency and methods for cleaning and disinfection of facilities, LAFW work surfaces, and critical sites on components and containers.

Cleaning and Disinfection

A robust cleaning and sanitization program is needed for controlled sterile-compounding areas to prevent microbial contamination of drug products. Air filtration, readily cleanable, non-porous surfaces, humidity controls, and cleaning and disinfecting procedures facilitate the maintenance of aseptic conditions. Prior to disinfection, cleaning is required to eliminate organic matter from surfaces that reduce the effectiveness of disinfectants. Table 2 of *USP Chapter <797>* specifies the minimum frequency for cleaning and disinfection of compounding areas. For example, an LAFW is sanitized at the beginning of each shift with a residue-free agent, such as 70% IPA; floors are mopped daily. Residue-free antiseptics are used to decontaminate human skin and exposed tissue before entering a controlled area. Finally, sterilants may be used to sterilize surfaces and materials used in compounding. While rotating classes of disinfectants is a commonly accepted practice, it has not shown benefit in scientific studies. A rotation of daily 70% IPA with a weekly application of a sterilant, such as 10% hydrogen peroxide, is a realistic rotation of disinfectants in clean areas. Non-shedding absorbent pads are suitable for protecting surfaces from spills of radioactivity. The following definitions apply to this chapter:

Antiseptic— An agent that inhibits or destroys microorganisms on living tissue.

Cleaning Agent—An agent for the removal of residues that may inactivate sanitizing agents or harbor microorganisms.

Disinfectant—A chemical or physical agent that destroys or removes vegetative forms of harmful microorganisms when applied to a surface, but not necessarily their spores.

Sanitizing Agent—An agent for reducing the number of microbes on surfaces.

Sporicidal Agent—An agent that destroys bacterial and fungal spores when used in sufficient concentration for a specified contact time. It is expected to kill all vegetative bacteria.

Sterilant—A liquid or vapor-phase agent that destroys all forms of microbial life.

Microorganisms differ greatly in their resistance to disinfection agents. A descending order of resistance of clinically significant bacteria is listed in Table 3.

Table 3

Resistance of Some Clinically Important Microorganisms to Disinfectants (Listed in Order of Decreasing Resistance)	
Microorganism Type	Examples
Bacterial spores	<i>Bacillus</i> spp. and <i>Clostridium sporogenes</i>
Mycobacteria	<i>Mycobacterium tuberculosis</i>
Nonlipid-coated viruses	Poliovirus and rhinovirus
Fungal spores & vegetative molds & yeast	<i>Trichophyton</i> , <i>Cryptococcus</i> and <i>Candida</i> spp.
Vegetative bacteria	<i>Ps. aeruginosa</i> , <i>Staphy. aureus</i> and <i>Salmonella</i> spp.
Lipid-coated viruses	Herpes simplex virus, hepatitis B, and HIV

USP Chapter <1072> *Disinfectants and Antiseptics* describes the effectiveness of disinfectants and how they are used. Table 4 classifies chemical disinfectants by chemical type. The effectiveness of a disinfectant depends on its intrinsic biocidal activity, concentration, contact time, nature of surface disinfected, hardness of water diluents, and amount of organic residue on the surface, and the type and number of microorganisms present. These conditions must be considered when selecting a disinfectant for compounding areas. The use of 70% IPA solution is commonplace because it rapidly destroys vegetative bacteria, those bacteria in an active growth cycle. Spray bottles of 70% IPA should be readily available for disinfecting supplies removed from shipping cartons.

Table 4

General Classification of Antiseptics, Disinfectants, and Sporicidal Agents		
Chemical Entity	Classification	Example
Alcohols	General purpose	70% Isopropyl alcohol (IPA)
Chlorine & Na hypochlorite	Sporicidal agent	0.5% Sodium hypochlorite
Hydrogen peroxide (H ₂ O ₂)	Liquid sporicidal agent; antiseptic	10 % solution; 3% solution
Peracetic acid	Liquid sterilant	0.2 to 1% peracetic acid
Quaternary ammonium compd.	General purpose disinfectant	Benzalkonium chloride

Sufficient exposure to hydrogen peroxide solutions, such as Spore-Klenz®, provides operator-safe sporicidal activity. Both are low-cost and leave little if any residue. Concentration, contact times and use conditions for disinfectants must be described in the relevant written procedures and followed to assure their effectiveness.

Spore-forming organisms are often found in sterility non-conformance investigations. Examples include fungi (*Aspergillus* and *Penicillium* spp.) and *Bacillus* species that form endospores, forms of bacteria that are highly resistant to adverse environmental conditions and disinfection. Spores are

readily transported by air currents and rafted on airborne particles. Should these microbes settle on unprotected critical sites and compounding surfaces, 70% IPA will not provide effective sanitization, because the alcohols are ineffective against *Bacillus* spores. Hydrogen peroxide $\geq 10\%$ is a strong oxidant that attacks lipid membranes, DNA and essential cell components, but an hour's contact time may be required to sterilize, i.e., kill both vegetative microbes and spores. *Bacillus* endospores are discussed in a convenient online microbiology text.²³

The type of bacteria found in an investigation provides a clue to their origin. *Staphylococcus* and *Propionibacterium* species are always found in skin tissue, so their presence implicates human sweat as a likely source of this type of bacteria. IPA 70% quickly kills vegetative microbes such as *Staphylococcus*, 4-to-5 log reductions in 1 minute of exposure, by means of denaturing protein. Molds proliferate in hot, humid conditions, particularly in the presence of $\geq 70\%$ relative humidity.

Critical Sites: Syringes, Needles and Vials

A critical site is any opening or surface that can provide a pathway between the sterile product and the environment. Examples include the tip of a needle, rubber stopper and ribs of the plunger on a syringe. Schneider²⁴ has illustrated techniques relevant to critical site protection.

A **syringe** has two basic parts, barrel and plunger. The plunger, which passes inside the barrel of the syringe, has a flat disk or lip for manipulation at one end and a cone shaped rubber piston at the other. The plunger is a critical site because it traverses within the critical area of the syringe barrel. Proper techniques must be employed while manipulating the plunger to avoid contamination of the sterile drug components being handled via touch contamination of the plunger. Ideally, for this reason, only sterile syringes should be used for a single critical manipulation in which the volume drawn into the syringe should be limited to approximately one-half of the maximal syringe volume. If syringes are filled to the maximum volume, there is an increased likelihood that the seal between the rubber piston and syringe barrel will be compromised (e.g., resulting leakage of air or liquid) and lead to the contamination of the drug component being manipulated. The top collar of the syringe barrel helps prevent the syringe from slipping during manipulation, while the tip provides the point of attachment for a needle. Many syringes have a locking mechanism at the tip, such as a Luer lock, that secures the needle within a threaded ring; others hold the needle by friction alone. The syringe tip (a critical site) must not be touched. Syringes may or may not have a protective cap on the Luer lock fitting to prevent critical site contamination. If a syringe, as packaged by the manufacturer, has no cap on the Luer lock

fitting, the overwrap should be removed in the LAFW and carefully handled until fitted with a sterile cap or sterile needle.

Syringes are sterilized, assembled and individually packaged in paper over wraps or plastic covers. The sterility of the contents is guaranteed so long as the outer package remains intact. Therefore, packages should be inspected to eliminate damaged goods. The syringe package should be opened at the edge of the laminar flow hood to maintain sterility in subsequent steps. If syringes are removed from their protective cover in anticipation of use at a later compounding period, an ISO Class 5 environment is the only suitable area for package removal, and they should be stored in a sanitized plastic container. Syringe and needle covers should be opened by peeling the cover from the end rather than bursting open the package with force on components.

Needles are also available in a variety of sizes. Needle size is designated by two numbers for gauge and length. The gauge of the needle corresponds to the outside diameter of the needle and ranges from 30, the smallest, to 13, the largest. The larger the gauge, the smaller is the bore of the needle. Length of a needle shaft is measured in inches, usually 3/8 to 3½ inches. Needles consist of two parts: the shaft and the hub. The tip of the needle shaft is finished to form a point by beveling, or slanting the hollow tube that is the needle. The needle point is called the bevel tip and the opposite end of the slant is called the bevel heel. Needles are sent from the manufacturer individually packaged in paper and plastic overwraps to maintain sterility of the contents while intact. Any damaged packages should be discarded. Needle packages should be opened within the laminar flow hood.

A needle shaft is usually metal and is lubricated with a sterile silicone coating. For this reason, needles should never be swabbed with alcohol. No part of the needle other than its protective cover should be touched to avoid compromising its sterility. The protective cover should be left in place until the needle and/or syringe is to be used, as when withdrawing fluid from a vial. When the protective cover is removed to perform an aseptic manipulation and there is a need to temporarily replace the cap to protect the sterile needle prior to a subsequent manipulation, great care must be taken to maintain the sterility of the cover and to avoid touch contamination of the sterile needle while replacing the cover.

A **vial** is a glass or plastic container with a synthetic rubber stopper secured to the vial by an aluminum seal that is crimped around the top. Ideally, there should be a removable cover (flip-top) attached to the center of the seal, because it minimizes surface contamination of the porous stopper during storage.

An unprotected stopper puncture area is particularly soiled, thus it is necessary to carefully disinfect all vials prior to puncture.

It is not acceptable to only spray the top of the rubber stopper; the surface must be scrubbed to minimize particulate matter, microbes or any machine oil that may have been deposited during the sealing of vials. The correct technique is to grasp the alcohol swab and, using firm strokes, wipe the stopper several times with strokes going in the same direction. Scrubbing back and forth and over the stopper is discouraged because material just removed on one swipe may be re-deposited on a subsequent swipe in a different direction. If several vials are to be swabbed at the same time, it is acceptable to use a single alcohol swab, so long as a clean, unused portion of the swab is used on each item. As with scrubbing down the interior of the laminar air flow hood, this swabbing is effective in two ways. The physical act of swabbing removes surface contamination and the IPA acts as a disinfecting agent. The residual sanitizer remaining on the surface of the stopper after swabbing should be allowed to dry before entry into the vial. Ideally, this cleaning procedure should leave the stopper quite wet so that the contact time is maximized. Immersion of a vial in an IPA-saturated, lint-free wipe is acceptable for decontaminating a number of vials at the same time.

When the hollow needle is inserted through the rubber stopper using improper technique, it is likely to punch out a piece of the rubber stopper, called a “core.” The core can be deposited in the vial or drawn back through the needle into the syringe. To prevent core formation the needle should be inserted in such a way as to penetrate the rubber closure at the same point with both the tip and heel of the bevel. This may best be accomplished by first piercing the rubber closure with the bevel tip and then applying light lateral pressure towards the bevel while applying firm downward pressure to insert the needle.

Decontamination of Reusable Shields

The cost of unit dose syringe shields (pigs) necessitates their recovery for reuse. The return of pigs from patient-care and treatment areas poses a potential for spread of human pathogens. Pigs must be cleaned and disinfected like any other equipment prior to being placed in the ISO Class 5 area.

Cleaning and disinfection to destroy viral and bacterial contamination must occur outside of the ISO Class 8 compounding area. The effectiveness of disinfection procedures against expected pathogens should be validated and documented.

CONTROL OF AIRBORNE CONTAMINATION

Evidence suggests that airborne microbes are spread in air by “dust” and by “nuclei droplets,” which are dried products of bacteria and saliva expelled from the mouth. Bacteria are also rafted into an area on skin scales. A healthy human sheds about 10 million skin scales daily and many of them carry microbes.²² The presence of disease, infections and wounds can add to microbial load. Therefore, **personnel are the greatest source of microbe-carrying particles (MCPs) and the most difficult factor to control in aseptic areas.**

Air Quality Classification

ISO Class 5 air sources, such as LAFW units, are designed and environmentally controlled to minimize airborne contamination contacting critical sites, earlier defined as any opening or surface that may expose an aseptic process to the environment. The required air quality of air increases with the criticality of an aseptic process. Air quality is defined by the concentration of particles as determined by a quantitative air sampling device. The International Organization of Standardization (ISO) classification of particulate matter in ambient air is used to define air quality (See Table 1). Routine radiopharmaceutical manipulations are done in an ISO Class 5 (formerly Class 100) LAFW that are located in an ISO Class 8 buffer area. Wagner²⁵ has reviewed the use of barrier isolators that may be useful for radio-labeling of cells.

Primary Engineering Controls

Laminar flow describes air that moves in a confined space with uniform speed along parallel lines, also described as unidirectional flow. Air flow in an LAFW must have a velocity of 90 feet per minute, $\pm 20\%$, and must be certified as ISO Class 5 air quality by tests for air flow velocity and filter integrity.²¹ Recertification of hoods and buffer areas must occur at six-month intervals. Proper maintenance includes changing prefilters, where applicable, and monitoring air-flow gauges for proper performance of the containment system.

Horizontal laminar flow hoods operate by first drawing ambient room air through a prefilter by means of an electrical blower within the hood. The prefilter removes only gross contaminants and should be cleaned and checked for replacement on a regular basis. Prefiltered air is then pressurized within a plenum to assure that a consistent distribution of air flow is presented to the final filtering apparatus. Constituting the entire back portion of a hood’s work area, this High Efficiency Particulate Air (HEPA) filter removes 99.97% of the particles that are 0.3 micron or larger, thereby eliminating

airborne microorganisms. The underlying principle of the laminar air flow hood is that the constant flow of approximately 90 linear feet per minute across the work surface physically sweeps the work area and minimizes the entry of lower-quality room air.

Vertical laminar air flow workbenches utilize a vertical flow of filtered air in which HEPA filtered air emerges from the top and passes downward through the work area. Vertical units are preferred for nuclear pharmacies because they are amenable to placement of lead-glass shields or other protective devices for the operators without serious disruption of laminar air currents. Air recirculates inside the hood to facilitate scrubbing of particulate matter.

Operators must be trained to work in a LAFW without allowing materials in the hood to disrupt the laminar flow at a critical site.²⁴ All work in a LAFW must be done at least six inches inside the hood to avoid exposure to room air. The basic principle of laminar air flow hood utilization is that nothing must interrupt the flow of air between the HEPA filter and critical site encompassing the sterile product. When a foreign object is between a critical site and HEPA filtered air, there is a possibility that contaminants from the foreign object may be introduced into the sterile product. Also, the surfaces of non-sterile components (packaging) must be thoroughly disinfected before entering the LAFW.

The LAFW should remain on continuously or be turned on at least 30 minutes before use. Begin sanitizing a LAFW with 70% isopropyl alcohol (IPA) or hydrogen peroxide, with a non-shedding wipe soaked with disinfectant, by wiping the sides of the hood followed by wiping the working surface; the wiping motion is from back to front for all panels.

Environmental Monitoring (EM)

Environmental monitoring is used to assess proficiency of aseptic technique, adequacy of cleaning and disinfection practices and efficiency of environmental controls for removing airborne particles. The current version of *USP Chapter <797>* stipulates the evaluation of airborne microorganisms in the controlled air environments (ISO Class 5, 7 or 8 areas) to be performed using electronic air samplers or by exposing sterile nutrient agar plates for a suitable time frames. The 2006 proposed revision of *USP <797>* relies upon electronic air samplers rather than settling plates to assess viable, airborne particulates.

A **proposed** assessment of EM is the requirement for glove-fingertip sampling. Studies have shown that inadequately sanitized gloves are the most likely source of critical-site contamination by cleanroom personnel. Contact agar plates are used to sample gloved fingertips outside of the ISO Class 5 area after a work period. If an established action level is exceeded, a review of procedures for disinfection of components (shields, package surfaces, etc.) and work surfaces, hand hygiene, garbing and all other work practices would be necessary. The ultimate standard for nuclear pharmacy has yet to be determined..

Other data that must be documented and evaluated are the performance of primary (e.g., LAFWs, CAIs and BSCs) and secondary engineering controls.^{25,26} Testing and validation documentation of every unit and area must be kept in a readily retrievable manner and systematically reviewed to show that certification results are within expected specifications.

PERSONNEL CLEANSING AND GARBING

The careful cleansing of hand and arms, and correct donning of cleanroom garb comprise the first step in preventing microbial contamination.²⁴ Personnel must also be competent and highly motivated to perform flawless aseptic manipulations of components.

Hand Hygiene

Compounding personnel are the focus of contamination control because almost all microbes in the cleanroom are of human origin. Aerobic bacterial counts on human skin are in the range of 10^4 -to- 10^6 cfu/cm². Personnel shed about one million organisms per hour. Clean hands and sanitized gloves are the most effective way to prevent spread of pathogens in healthcare settings. Current hand hygiene guidelines were developed by the Centers for Disease Control and Prevention (CDC) in collaboration with three stakeholder injection-control associations.²⁷ These guides were incorporated into the new hand hygiene and garbing requirements of *USP <797>*.

The CDC hand hygiene guide defines *alcohol-based hand rub* as an alcohol-containing preparation designed for application to the hands for reducing the number of viable microorganisms on hands. Such preparations usually contain 60%-90% ethanol or isopropanol (IPA). An *antiseptic handwash* is washing of hands with water and soap or other detergents (cleaning agents) that contain an antiseptic agent, antimicrobial agents including alcohols, chlorhexidine, chlorine and quaternary ammonium

compounds. Thus, *hand hygiene* is a general term that applies to handwashing, antiseptic handwash, antiseptic hand rub, or pre-garb hand antiseptics.

The antimicrobial activity of alcohols is attributed to denaturing proteins. Alcohol-based hand rubs are available as low viscosity rinses, gels and foams. Isopropanol 70% is commonly used because it is more potent than 100% concentrations in that proteins are not denatured easily without water. Alcohol disinfectants have excellent germicidal activity against gram-positive and gram-negative bacteria, including multidrug-resistant pathogens, *Mycobacterium tuberculosis*, most fungi and certain enveloped (lipophilic) viruses. (see Table 3) Limitations of alcohols includes the long contact time necessary for broad cidal activity, up to 10 minutes for *Mycobacterium tuberculosis*, and their lack of persistence due to rapid evaporation. The greatest limitation is that alcohols are not reliably sporicidal against the spore-forming bacteria, such as *Clostridium* and *Bacillus* spp. The volume of alcohol necessary for antiseptics varies, but as a general guideline, if hands feel dry after rubbing hands together for 10-15 seconds, an insufficient volume was likely applied. Frequent use of alcohol preparations may cause skin dryness unless emollients or other skin-conditioning agents are added to the cleaning process.

While alcohol-based hand rubs provide a cost effective antiseptic, other products are available. Products for potential use must be evaluated for relative efficacy of antiseptic agents against various pathogens and acceptance of hand hygiene products by personnel. Characteristics of a product (either soap or alcohol-based hand rub) that can affect acceptance by personnel include its smell, consistency (i.e., "feel"), and color

Dispersion of particles from skin rashes or sores, sunburn, conjunctivitis, respiratory infection or cosmetics must be suitably controlled or eliminated by excluding these conditions from the work area. Proper hand hygiene includes removing debris from underneath fingernails using a nail cleaner, under running warm water, followed by vigorous hand washing. Jewelry (not ring badges) should be removed because gram(-) bacilli are frequently found under rings.

Hand hygiene promotion includes in-service education, workshops and lectures, automated dispensers, ready access to sinks, routine observation and performance feedback, and reminders in the workplace. It is critical for CSP formulators to recognize the need for good hygiene, know and promote the techniques and understand the expectations for patient care.

Personnel who prepare radiopharmaceutical CSPs are generally compliant with glove requirements because of radiological health issues, and more recently the emergence viral pathogens such as Hepatitis C and HIV. Good glove hygiene is a challenge because of the tendency to wear the same gloves for long time periods and to overlook the need for frequent re-sanitization of gloves and work materials. Control of touch contamination requires an emphasis on continuous re-sanitization and ready availability of IPA spray bottles. Personnel must recognize when sterile gloves are needed for a task.

Garbing

Before entering the ISO Class 8 clean area, personnel must remove personal outer garments such as bandannas, jackets, hats. Personnel must don protective apparel from the dirtiest to the cleanest. Ideally, dedicated, inside work shoes should replace outside shoes which maybe an enormous contributor of bacteria. Shoe or shoe covers are followed by head and facial hair covers. Hands and arms are washed to the elbows for at least 30 seconds with antimicrobial soap, ideally in an anteroom; scrub brushes are not desirable because they induce irritation. Hands should be dried with non-shedding towels or an electric dryer. Upon donning a clean, dedicated lab coat, and non-shedding gloves that fit around the wrist, sanitize gloves by spraying 70% IPA and rubbing hands vigorously. Gloves, either sterile or non sterile, re donned last and after hands are dry. Gloves become contaminated when they contact nonsterile items or surfaces during compounding, so repetitive IPA spraying and rubbing of hands, followed by drying, greatly reduce bacterial levels. Spray bottles of 70% IPA should be readily available to facilitate continuous disinfection. Personnel must be trained and evaluated to avoid touching critical sites with contaminated gloves. When personnel must temporarily leave the ISO Class 8 area, the exterior gown might be temporarily stored, but shoe, hair and face covers should be replaced with new ones before reentry.

DESIGN OF A NUCLEAR PHARMACY

There are multiple ways to design or redesign a nuclear pharmacy in an effort to address *USP Chapter <797>* requirements for compounding sterile preparations for use in nuclear medicine practice. Recently, Wittstrom described a conventional nuclear pharmacy floor plan (Figure 1) designed primarily to meet the requirements of the Nuclear Regulatory Commission (NRC) for handling of radioactive materials.²⁸ The floor plan includes several important features, such as a labeling room with laminar air flow hoods and dose drawing stations in laminar air flow to facilitate aseptic processing of both radiopharmaceutical and pharmaceutical preparations. However, due to the more

recent establishment and revision of *USP Chapter <797>*, this floor plan is in need of review and possible redesign to more specifically address the current standards for compounding sterile preparations. Therefore, this discussion section will focus on the redesign of this representative nuclear pharmacy service facility to provide some examples of the types of changes that may be required to facilitate compliance with the emerging *USP Chapter <797>* requirements.

As is true for any pharmacy designed for compounding sterile preparations, a nuclear pharmacy should be logically arranged with areas designated for specific functions with the CSPs area(s) located in an engineering controlled environment away from ordinary restricted work areas which are not utilized for aseptic processing. The physical layout of each nuclear pharmacy may vary in size and design; however, the aseptic compounding areas must include certain key features.

Prior to the implementation of *USP <797>* as an enforceable standard, it was common practice to divide a nuclear pharmacy into two areas; one unrestricted and the second restricted as shown in Figure 1. The unrestricted areas may include offices, a conference room, and other employee areas where the general public is welcome without safety restrictions associated with radioactive materials or aseptic processing. Restricted radioactive materials areas include any work areas which support the general handling or storage of radioactive materials and these areas may or may not be appropriate for aseptic handling activities. Radiation safety regulations require that only trained radiation workers have access to areas where radioactive materials are handled and stored. The current sterile compounding guidelines stipulate that only trained and qualified personnel have access to those areas additionally controlled for aseptic processing. This adds an extra level of personnel training, testing and documentation as well as documentation of compliance with the environmental standards requirement.

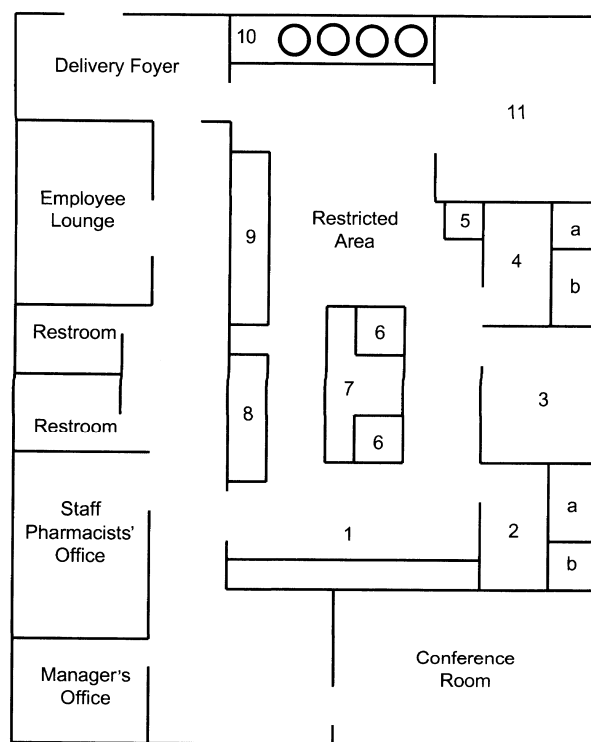


Figure 1 – Conventional nuclear pharmacy floor plan. (1) Prescription processing area, (2) labeling room with laminar flow hoods, (3) generator room, (4) radioiodine room with (a) fume hood and (b) exhausting glove box, (5) refrigerator / freezer, (6) dose drawing station in laminar flow hood, (7) wrapping area, (8) quality control area, (9) DOT area, (10) waste processing area, (11) waste storage room. (Figure reproduced with permission of author.²⁸)

In considering the conventional nuclear pharmacy floor plan (Figure 1) further, there are several possible problem areas with regard to USP <797> compliance. The major overall concern is the apparent absence of secondary engineering controls necessary for establishing and maintaining the ISO Class 8 environment now required for compounding sterile radiopharmaceutical preparations. The labeling room represents the area of greatest concern given that this room is designated for medium-/high-risk level activities. The interface between the compounding (aseptic processing) area and the waste processing area is another major concern. Finally, there may be some potential use issues related to the generator room and the radiopharmaceutical dose-drawing stations, however, these latter concerns can be addressed rather easily given their central location in the laboratory.

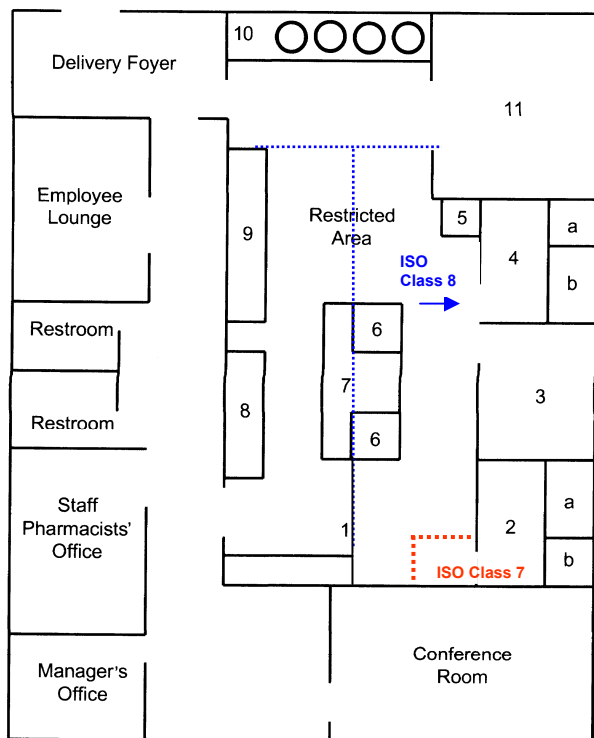
The conventional floor plan is logically arranged to provide for optimal and efficient work flow patterns, however, these work patterns do not necessarily support the attainment or maintenance of an ISO Class 8 environment. Secondary engineering controls **may be** required to create an ISO Class 8 or greater environment to surround the primary (ISO Class 5 LAFW) engineering controls in the compounding area(s). USP 797 does not require major facility reconstruction or that sophisticated cleanrooms be installed. What the guideline does require is environmental controls – specifically, a separate area for compounding that meets a defined level of cleanliness, and monitoring to ensure that control is maintained. An ISO Class 8 compounding area is the primary environmental control requirement.

The first step is getting a baseline assessment on the existing facility to determine what remediation steps, or facility and procedural redesign, will be required to meet the environmental controls. A baseline analysis might include:

1. Housekeeping: routine cleaning and sanitizing procedures to maintain facility and environmental quality.
2. Air movement patterns: currents from opening doors or HVAC
3. Air quality sampling
4. Personnel traffic within compounding area
5. Production activities.

The net result of the USP 797 guidelines is that sterile mixing take place in a properly maintained laminar airflow hood (ISO Class 5) situated in a relatively clean room (ISO Class 8). For most

pharmacies, this is neither difficult nor unreasonable. In some cases, individual interpretations of this requirement have made it seem more onerous.



A controlled compounding environment could be created rather easily by installing a barrier (dashed lines in Figure 2) between the uncontrolled and controlled engineering areas. Dependent upon the physical aspects of the facility and the training of personnel, the “barrier” could be a simple mark on the floor; soft barrier walls or solid hard walls. The barriers would require controlled pass thru ports at key locations such as the area where drawn doses are transferred to the wrapping area which is outside the ISO 8 environment. If needed, ceiling mounted HEPA filter fan units could be added to further clean the air in the controlled isolated environment to the required level.

Figure 2 – Conventional nuclear pharmacy floor plan with added engineering controls. Blue line divides uncontrolled environment from controlled environment. Red lines outline ISO Class 7 area of labeling room. (1) Prescription processing area, (2) labeling room with laminar flow hoods, (3) generator room, (4) radioiodine room with (a) fume hood and (b) exhausting glove box, (5) refrigerator / freezer, (6) dose drawing station in laminar flow hood, (7) wrapping area, (8) quality control area, (9) DOT area, (10) waste processing area, (11) waste storage room. (Figure reproduced with permission of author.²⁸)

As indicated in Figure 2, a medium-/high-risk level aseptic processing room (marked 2) is appropriately sequestered from general work traffic patterns and the entry point is preceded by an ante area, which serves to keep the room as clean as possible at all times. The ante area is used for hand sanitizing and donning appropriate attire prior to entering the aseptic

processing room. Open-container and open-transfer processes requiring ISO Class 5 air environment and a buffer area are performed in this room. There are two ISO Class 5 primary engineering control devices in the room that are employed for medium or high-risk level aseptic processing procedures. These control devices²⁵ are critical for medium-risk procedures or high-risk procedures such as compounding I 123 MIBG using nonsterile ingredients. When biological samples are processed in these control devices, special SOPs are required to disinfect and sanitize the devices both prior to and following their use for each blood cell labeling procedures.

The interface between the waste processing and the aseptic processing areas of the nuclear pharmacy represents another major concern with regard to the overall cleanliness. The waste processing area may serve multiple functional purposes; however, the most important one is to provide a place to safely process and store both internally or externally generated biohazardous radioactive waste materials until they can be disposed in a proper manner. Of these waste materials, those generated and returned by hospitals and clinics represent a substantial hazard to general safety because their history is poorly documented. Therefore, one must always assume that externally generated waste (e.g., needles, syringes, and absorbent pads), their immediate containers (e.g., syringe pigs) and even their packing materials and transport containers are biologically contaminated, and if improperly handled, they may place an aseptic processing operation at risk. In this example, additional facility changes are needed. For example, it would be most appropriate to create a physical barrier between the aseptic processing and waste processing areas as noted in Figure 2. The barrier used should support the ISO Class 8 area of the compounding area. This might involve a hard wall or perhaps a glass wall atop a cabinet counter top with a pass thru area so that waste generated in the aseptic processing area can be easily transferred to the waste processing area without personnel leaving the controlled environment.

The generator room or area is the site within the restricted and controlled area of the nuclear pharmacy where multiple ^{99m}Tc generators are stored and used on a daily basis. A typical nuclear pharmacy maintains many multi-Curie generators in active inventory at all times, and each one may be in use for up to two weeks. Auxiliary lead shielding, needed to minimize radiation exposure, adds to the bulk. Due to the relative mass of each generator, the large number used, and the auxiliary shielding required for each generator, it is both impractical and unsafe to require that these heavy items be routinely moved wholesale solely to perform cleaning and disinfection procedures by standard USP <797>. Regardless of the potential hazards associated with moving generators, each nuclear pharmacy operation must have procedures for keeping the generator area as clean as reasonably achievable. For example, it is entirely reasonable to have an SOP for cleaning in and around each auxiliary generator shield after an expired generator is removed from inventory and prior to replacing it with a new generator. For many of the same reasons, it is currently acceptable to locate and elute generators in an ISO Class 8 environment. If an existing generator room or area is less than ISO Class 8, a ceiling mounted HEPA filter fan unit may be installed to achieve this required ISO Class environment.

It is common practice for nuclear pharmacies to have multiple dose-drawing stations, which primarily consist of a LAFW with appropriate shielding and a radionuclide dose calibrator. In addition, the

LAFW may have external radiation shielding or removable shielding placed within the workbench to protect the operator. Shielded dose calibrator ionization chambers may also be placed in the LAFW and may be countersunk to facilitate cleaning and minimize the amount of space they occupy in the LAFW. These hoods are utilized for all closed-system low-risk level compounding which typically includes the reconstitution of commercially available Tc 99m kits with sodium pertechnetate Tc 99m and saline as necessary for dilutions, drawing a quality control sample and dispensing unit dose radiopharmaceuticals in sterile syringes. After each unit dose is drawn, the syringe is placed into a syringe pig and then transferred to the wrapping area where it is subsequently processed for shipping and delivery.

The redesigned nuclear pharmacy, as shown in Figure 2 is divided into three types of work space which include unrestricted areas, restricted radioactive materials areas and restricted engineering controlled aseptic processing areas. The restricted engineering controlled area, a subunit of the restricted radioactive materials area, is strictly dedicated to the aseptic processing of sterile radiopharmaceutical and pharmaceutical preparations. It is critically important to recognize that radiation training alone does not qualify personnel to enter engineering controlled areas. Current sterile compounding guidelines specify that only trained and qualified personnel may have access to the engineering controlled areas of the nuclear pharmacy where aseptic processing is undertaken. For this reason, a redesign project must include greater emphasis on limiting access to and traffic in restricted environmental controls areas to trained and qualified personnel only.

PERSONNEL MANAGEMENT

Policies and Procedures

Personnel are more likely to perform to expectations if there are standard operating procedures (SOPs) that clearly describe their tasks and policies that set the tone for quality performance. A good policies and procedures manual can promote the safe, efficient and uniform performance of all pharmacy personnel and functions.²⁹ Regarding responsibility of compounding personnel, they are clearly responsible for ensuring that radiopharmaceutical CSPs are compounded according to their best professional judgment and training, local procedures, applicable pharmacy regulations, *USP Chapter <797>* and applicable vendor use instructions, such as package inserts. These performance responsibilities include maintaining appropriate cleanliness conditions and providing labeling and supplementary instructions for the proper use of these drugs in nuclear medicine.

Personnel Training and Evaluation in Aseptic Manipulation Skills

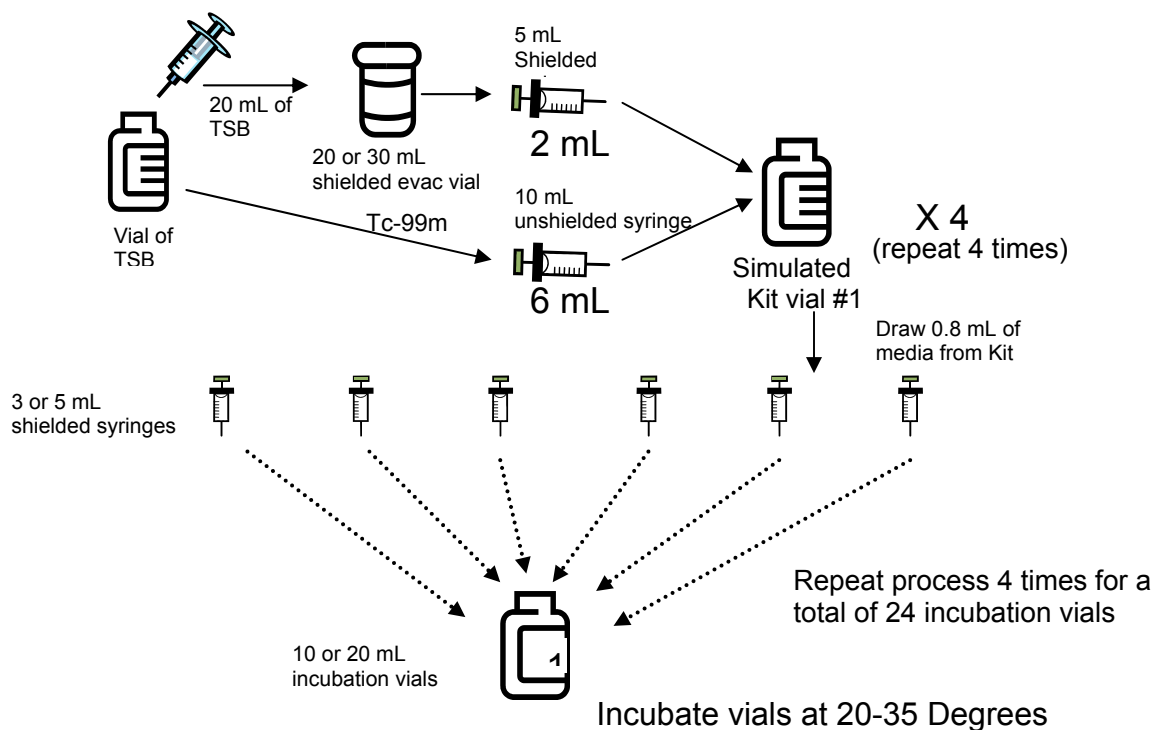
People are the greatest source of contamination in a compounding facility. The best of facilities and procedures will not yield sterile preparations unless compounding personnel are trained and motivated to do their job, professionally, and to the best of their abilities. Personnel who prepare radiopharmaceutical CSPs must be trained conscientiously and skillfully by expert mentors who employ didactic material, instructional aides and professional publications that describe aseptic manipulations. Training and continuing education experiences must be documented and reviewed on a scheduled basis.

The didactic and experiential training in aseptic techniques must be evaluated by a media-fill challenge testing plus oral or written assessment of understanding. Trissel and coworkers have published on the impact of such training on cleanroom behavior in the hospital setting.³⁰ Their evaluation of training results and corrective actions, including the use of frequently sanitized or sterile gloves, led to a significant reduction in failed media-fill studies at a medium-risk level.

The assessment of sterile compounding skills by simulated media fill, according to a carefully crafted SOP and assessment tool, is an essential component for training and qualification of a nuclear pharmacist or technologist and for validating an aseptic process. The media fill should simulate basic operations in a nuclear pharmacy, including preparation of a Tc 99m kit and drawing multiple unit doses. Soybean-Casein Digest Medium (SCDM) is substituted for Tc 99m components to simulate representative radiopharmaceutical compounding. The facility's existing procedures for cleaning and disinfection, garbing, aseptic technique, etc., should be used in the media fill exercise. The authors recommend a variation of a simulated media fill procedure (Figure 3) being considered by the Nuclear Pharmacy Section of the APhA.³¹ In this test, a shielded 1-mL and a 3-mL aliquot of media simulate kit compounding by Tc 99m eluate rehydration and saline dilution. Finally, six unit doses are drawn from the kit vial and injected into an incubation vial. This protocol is conducted in 4 replicates in one work period to introduce a fatigue factor. The 4 kit vials and 4 incubation vials (the accumulation of six unit doses, each) are incubated for at least 14 days at 20°C to 35°C. The media vials are inspected over a 14-day period for turbidity or other signs of microbial growth. The absence of growth and satisfactory completion of other requirements yield a qualified person in aseptic technique. Requalification is an annual requirement. This procedure is a relatively insensitive means for

assessing aseptic technique, so it should never be used to validate marginal cleanroom behavior. Rather, this procedure should emulate the spirit and guidance of *USP Chapter <797>*.

Figure 3 - Simulated media fill for Tc 99m radiopharmaceuticals. Two syringes representing pertechnetate and saline reconstitute a kit vial. Six unit doses are transferred to a collection vial, in four replicates. The kit and incubation vials are incubated and observed after 14 days. This procedure was adapted from www.pharmacist.com.



ACHIEVING STERILITY OF COMPOUNDED RADIOPHARMACEUTICALS

Sterilization

Radiopharmaceuticals that are prepared from nonsterile materials must be sterilized by filtration, steam or irradiation, and be tested for microbial and endotoxin contamination; all methods and procedures must be validated. Examples of such products include ^{123}I -iobenguane (MIBG), PET drugs and investigational agents prepared on site; *USP Chapter <797>* specifically refers preparation of PET drugs to *USP Chapter <823>*. Sterilization is the complete removal or eradication of microorganisms, and is discussed elsewhere.³² Steam is the definitive sterilization method when a validated and documented cycle is used. Most radioactive drugs are heat labile, and thus, sterilized by aseptic processing, which requires passing the nonsterile product through a sterilizing membrane filter and sterile pathways into sterile containers. Aseptically sterilized products also require end-product assessment for microbiological purity. Upstream components and materials must have little or no bioburden (live

bacteria) because some microbes generate endotoxin, specifically, gram-negative bacteria that survive in low-nutrient environments.

Sterile membrane disc filters are commercially available with certification for sterility, apyrogenicity, extractables and capacity to retain challenge microbes (*Brevundimonas diminuta* at a minimum concentration of 10^7 organisms/cm³).²⁹ Microbial validation of an aseptic process and qualification of personnel require a simulation of the process using Soybean Casein Digest Medium (SCDM) and incubation of down-stream components and the simulated final product.

Membrane Integrity Test

A successful bubble-point test is the best way to know that a membrane-sterilized product was actually sterilized because it verifies that the filter was free of leaks or defects that would allow passage of bacteria. This test is based on the principle that liquid is held in the capillary structure of the membrane by surface tension.²⁹ The minimum pressure required to force the liquid out of the capillary space is a measure of the largest capillary diameter. In this test, retained fluid is forced from filter pores by nitrogen or air pressure applied from the upstream side to the degree that the capillary action of that particular pore is overcome. A filter vendor determines the bubble point pressure for its product. Bubble-point specifications for a water-wet membrane are approximately 50 psi. Pharmacists should subject the filter to slowly increasing pressure, through a calibrated pressure gauge, and confirm the bubble-point published by the vendor. It is critical to increase this pressure slowly so that tiny filter flaws will be detected. If a bubble-point test gives a result less than the stated specification, the filter should be re-wetted and retested, once. A second failure requires reprocessing by passing the product through a new filter assembly.

Devices for filter-integrity testing include a pressure source, (e.g., nitrogen tank) a calibrated pressure regulator and sufficient tubing to access the test site. There are also commercially available filter-integrity test kits that are useful for the small filters used in nuclear pharmacy practice. With the commercial test kit, a pressure gauge attached to a three-way stopcock is employed to measure the pressure held by the filter. The observed pressure can then be compared to the manufacturer's specification for pressure resistance. In the absence of these devices, at a minimum, one should check the membrane filter integrity by observing resistance when attempting to force a volume of air through the filter with a large syringe. Finally, the integrity test must be completed prior to patient administration and results documented in the batch production record.

Sterility Test Methods

Successful sterility testing requires aseptic sampling of an aliquot from the final container, suitable preparation in an ISO Class 5 LAFW suite and inoculation of media by qualified personnel within 24 hours of preparation, using PET drugs as a model.³³ The method should be consistent with *USP Chapter <71> Sterility Tests*. Prepared culture media in 8-mL volumes, having a Certificate of Analysis (CoA) for Growth Promotion Test and Sterility of Media, are convenient for sterility testing by direct inoculation. Soybean casein digest medium (SCDM) is a general nutrient media optimized for aerobic bacteria and fungi. Fluid thioglycollate medium (FTM) detects anaerobic and aerobic bacteria. The top, aerobic phase has resazurin dye to indicate its suitability; it is pink if oxygen is present. A tube of FTM may be heated once to regenerate anaerobic conditions if the pink phase occupies more than about one-half of a tube's volume. Media tubes must be checked upon arrival for evidence of leaks, contamination and sediment of particulates that might be later judged as bacterial growth. An outside sterility-test facility, such a hospital clinical laboratory, must use bacterial growth media specified in *USP Chapter <71>*.

Care must be taken to avoid contamination of a sterility test sample, especially if sampling occurs in other than a critical area. Sanitization of an LAFW with IPA, as previously described, reduces bioburden on surfaces to a very low level. During inoculation, the motion of opening a tube and removing the needle cover must be slow and deliberate, and exposed, critical sites must be directed toward the HEPA filter. These sites must not be shadowed by any other item or exposed to turbulence that stirs up particles. Documented evidence of good environment and technique is done by exposing settle plates of TSA (Trypticase soy agar, a solid form of TSB) during the inoculation process and using touch plates for the operator's fingertips. Finally, the LAFW is sanitized immediately afterwards to leave the hood in operational condition.

Interpretation of results is somewhat subjective. Media tubes are examined for cloudiness, precipitation and other evidence of microbial growth. An appropriate record form must document observation times, dates, results and identity of the operator. Microbial growth (positive) in a sterility test should prompt an investigation into the cause that includes speciation to organisms, interview of operators and review of all records. Speciation helps identify the source of contamination. For example, growth of fungi, mold or *Bacillus* species indicates airborne or dust borne spores, pseudomonads (*Ralstonia*) suggest water-borne contamination, coliforms indicate exposure to fecal matter (poor hand hygiene) and Gram (+) cocci indicate human touch, sweat drops or shed

contamination. An investigation into a non-conforming result test should be completed expeditiously. Although the root cause may not be identified, corrective action should be made to include more training, re-qualification of personnel, more effective sanitization and better environmental control.

Bacterial Endotoxins Test (BET) Methods

The classic gel-clot reaction of the *USP Chapter <85> BET* requires an hour's incubation period for four components (Table 4). A revision of the BET in 2001 simplified the gel-clot limits test so that an endpoint assay of the CSE-spiking tube (20λ) is only required at time of preparation. Detailed and illustrated descriptions of simplified methods appear elsewhere.^{34,35} Chapter <85> specifies a test for interfering factors because the LAL and endotoxin reaction requires pH neutrality and absence of interfering factors, such as citrate which chelate essential divalent cations. However, the BET has great sensitivity that allows substantial dilution of drugs to eliminate inhibiting conditions without compromising safety. Radiopharmaceuticals should be diluted at least 1:40 to make the BET robust (avoid inhibition) and reduce radiation exposure to the operator. The recovery of positive controls in three successive tests of a specific set of conditions constitutes validation of a BET method for a specific drug. Validation in gel-clot testing occurs when a specific dilution of a drug gives the same endotoxin endpoint in diluted product as one in water. Validation of a photometric test requires the recovery within 50 to 200% of a known amount of endotoxin spike in three batches of a diluted sample. The limit of detection (LOD) is the reagent sensitivity (λ, lambda) times the dilution factor. For example, the LOD for a BET is 2.5 EU/mL when lambda equals 0.0625 EU/mL and the radiotracer is diluted 1:40 prior to testing. Therefore, the correct way to report a conforming (pass) BET is to record a value that relates to the LOD, such as, <2.5 EU/mL for the example above.

Table 5

Gel-Clot Limit Test by USP <85> for a PET Radiopharmaceutical				
Tubes	Endotoxin	Sample Solution	No. Replicates	Expected Result
A (Drug)	None	Diluted PET drug	2	Negative ^e
B (PPC) ^a	2λ	Diluted PET drug	2	Positive ^e
C (PWC) ^b	2λ	LAL ^d Reagent Water	2	Positive
D (NC) ^c	None	LAL Reagent Water	2	Negative

Legend:^aPPC, the positive product control; ^bPWC, positive water control; ^cNC, negative control; ^dLAL, *Limulus* amoebocyte lysate; ^eResult is positive if the gel holds firm through a 180° turn; all other results are negative.

Rapid BET methods emerged due to a need to test injectable PET drugs. A novel pre-calibrated cartridge with kinetic chromogenic reagent (Endosafe® PTS system by Charles River Labs, Charleston, SC) is a photometric test for rapid, quantitative assay in less than 15 minutes over a range

of 5 to 0.05 EU/mL. In this case, lambda is the lowest point on the standard curve, 0.05 EU/mL. A cartridge has 2 channels each for measuring endotoxin and for assuring validity by PPCs. Diluted test solution is drawn through channels where it picks up dry reagents, including the endotoxin positive control. No CSE standards are necessary. Any endotoxin present, such as the positive controls, produces color that is measured by a spectrophotometer. The test is valid if criteria for precision and recovery of endotoxin controls are met and within specification. The system offers speed, objectivity and convenience.

ENFORCEABILITY AND RECOGNITION

Drug Enforcement Agencies

Enforceability of *USP Chapter <797>* is uncertain at the time of this writing, late 2006. There is a maze of regulations, guides and other documents from federal, state, professional associations and standard-setting organizations that have some impact on nuclear pharmacy practice.^{21,36}

As for the FDA, the Federal courts have not supported unilateral encroachment of this Agency into the practice of pharmacy. The FDA exercises the option to investigate public safety issues regarding certain compounded prescriptions that pose a hazard. The FDA exercises what it calls enforcement discretion, preferring to confront pharmacies whose preparation of items meets the Agency's definition of manufacturing. Generally, the FDA regulates parenteral products in accordance with a recent aseptic processing guidance.³⁷ The FDA also regulates PET drugs by a PET-drug CGMP guidance.³³

The Board of Pharmacy in each state must grapple with the changing environment for regulating sterile compounding. Predictably, they are taking different approaches to the implementation of the requirements set forth in *USP Chapter <797>*. Implementation activities can be generally categorized into four groups.²¹ Boards of Pharmacy in the first group of states interpret their existing laws and regulations as requiring pharmacies to comply with Chapter <797> even though there is no specific reference to the chapter; Louisiana and Massachusetts are examples in this first category. States in the second category have acted to change their law or regulation to specifically reference USP compounding standards or Chapter <797>, explicitly. States in this category include Indiana, New Mexico, South Carolina, Texas, Utah, Virginia, and others are close to joining this group. In the third category are Boards that have incorporated specific language from Chapter <797> into their regulations. States currently included in this category include Arkansas, Ohio and others. These states require compliance with selected tenets of Chapter <797> that were incorporated into the text of their

regulations, but do not refer to or require compliance with the Chapter. The fourth and final group consists of states that are continuing to review Chapter <797>, have appointed a task force to study the issues and recommend an action plan, or have decided not to take any actions to implement the chapter at the current time. Because of the many differing approaches States are taking with regard to recognizing, implementing and enforcing *USP Chapter <797>* compounding standards, pharmacists should contact their Board of Pharmacy directly to obtain the specific language appearing in applicable state laws and regulations.

The National Association of Boards of Pharmacy (NABP) is an independent association of Pharmacy Boards. NABP has Model Rules for Pharmacy Interns, Institutional Pharmacy, Pharmaceutical Care, Nuclear/Radiologic Pharmacy, and Sterile Pharmaceuticals. Significantly, NABP recently revised the Model Act to reflect the requirements of Chapter <797>.²¹ Revised Appendix C entitled, “Good Compounding Practices Applicable to State Licensed Pharmacies” sets forth the requirement for compounding pharmacists and pharmacies to practice in accordance with current USP-NF chapters on compounding and sterile product preparation. The Model Rules for Sterile Pharmaceuticals also include a comment recognizing three microbial risk levels for compounding activities, as currently identified in USP Chapter <797>. The NABP Model Act and Model Rules are enforceable only to the extent that they are implemented into law or regulation by the individual states.

Joint Commission on Accreditation of Healthcare Organizations (JCAHO)

In the April 2006 edition of *Joint Commission Perspectives*, the Joint Commission (JCAHO), the principal hospital accrediting organization in this country, clarified their expectations related to compliance with USP <797>.³⁹ The article states: “The Joint Commission will not survey for compliance with the details of USP 797. How ‘exacting’ the organization complies with the USP <797> guidelines and the suggested timeframes for compliance are based on organizational decision. An accredited organization can decide its compliance with USP <797> with advice from experts and stakeholders, such as the organization’s director of pharmacy, risk manager, facility manager, microbiologist, infection control staff, and legal counsel, taking into account state laws and regulations. If permitted by state laws, an organization may choose an alternative approach to a specific USP guideline based on review of literature or organizational studies.” Consequently, it is important to realize that JCAHO does not survey organizations for specific compliance with Chapter <797> and further does not interpret the Chapter’s specific requirements for a given practice setting.

For accreditation purposes, JCAHO surveyors will expect to see evidence of structures and processes that ensure safe practices for compounding sterile medications. Therefore, JCAHO considers *USP Chapter <797>* “a valuable set of guidelines – contemporary consensus-based safe practices – that describe a best practice for establishing safe processes in compounding sterile medications.”³⁹

Correspondingly, JCAHO expects healthcare organizations to review the procedures for preparing sterile medications in light of the Chapter, but does not require these organizations to implement the Chapter standards across the board. Except for those elements of Chapter <797> that are also contained in JCAHO standards, accredited organizations may choose to implement all or some elements of Chapter <797>. Implementation approaches may differ from those in Chapter <797> based on a review of literature or organizational studies that support maintaining current practices. JCAHO has not enforced USP Chapter <797> to the extent that was originally expected.³⁶

SUGGESTED READING:

1. *USP Chapter <797> Pharmaceutical Compounding – Sterile Preparations: Guidebook to Proposed Revisions*, The United States Pharmacopeial Convention; Rockville, MD: 2006. This guidebook contains the most comprehensive information on the content and the 2006 revision process for USP <797>.
2. Buchanan, Clyde E., and Schneider, Philip J. *Compounding Sterile Preparations, 2nd edition*, American Society of Health-System Pharmacists, Bethesda, MD. 2005. This soft-back book provides general information on the aseptic processing in the hospital setting.
3. Todar’s Online *Textbook of Bacteriology*. <http://textbookofbacteriology.net/bacteriology.html>. This website is a convenient source of well illustrated descriptions of microorganisms and other topics relative to microbiological control and other phenomena

Note: The *USP Chapter <797>* guidebook listed above is a companion document for this CE unit. The questions from this unit are taken from both sources, as a working knowledge of both is necessary for successful assessment.

SUMMARY AND CONCLUSIONS

USP Chapter <797> specifically applies to radiopharmaceuticals compounded in nuclear pharmacy practice. Compliance helps assure that sterility is maintained when compounding exclusively with sterile ingredients and components, or sterility is achieved when compounding with non-sterile ingredients or components. Cleanliness or quality of air in critical compounding areas, disinfection procedures, process controls and properly trained personnel constitute the foundation of microbial control. Finally, assessment of compounding-personnel practices and environmental monitoring provide evidence that aseptic processing is under control.

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QUESTIONS

1. The best way to control airborne contamination is to use:
 - A. a properly certified laminar air flow workbench.
 - B. the bubble point test.
 - C. a disinfection protocol with 70% isopropanol.
 - D. a pair of sterile gloves and sleeves.
2. A microorganism that is NOT spread by humans is:
 - A. mold, such as *Penicillium commune*.
 - B. *Escherichia coli*.
 - C. *Staphylococcus hominis*.
 - D. yeast, such as *Candida albicans*.
3. Electronic air samplers are used to monitor :
 - A. total particles on the workbench surfaces.
 - B. viable particles in the air.
 - C. total particles in the air.
 - D. viable particles on the workbench surface.
4. The minimum frequency for cleaning and disinfecting in the ISO Class 8 area is:
 - A. daily for a biological work surface.
 - B. weekly for floors.
 - C. weekly for walls and ceilings.
 - D. at the beginning of each shift for a vertical laminar air flow hood.
5. A significant limitation of 70% IPA (isopropanol) as a disinfectant is:
 - A. lack of bactericidal activity.
 - B. expense.
 - C. lack of sporicidal activity.
 - D. safety.
6. Alcohol-based hand rubs are:
 - A. more effective than plain soaps for reducing bacterial counts on the hands.
 - B. less accessible than sinks or other handwashing facilities.
 - C. most effective when composed of 100% IPA (isopropanol).
 - D. only effective if they are applied for ≥ 1 minute.

7. A nuclear pharmacy was closed after a contaminated cardiac imaging agent resulted in systemic infections in at least twelve patients. The infectious agent was:
- A. Hepatitis C.
 - B. *Enterobacter cloacae*.
 - C. *Escherichia coli*.
 - D. Human immunodeficiency disease.
8. A requirement for radiolabeling of a patient's white blood cells is:
- A. an ISO Class 7 compounding environment.
 - B. a dedicated environmental control area.
 - C. a compounding aseptic isolator.
 - D. initiation of a sterility test within 24 hours.
9. A simulated media fill used to validate personnel technique :
- A. uses of trypticase soy agar.
 - B. assesses personnel cleanroom behavior.
 - C. simulates conditions outside of the dose-drawing area.
 - D. is required every six months
10. An ISO Class 5 environmental area is:
- A. required for radiopharmaceutical compounding.
 - B. specified for removing syringe and needle packages from cartons.
 - C. the best place to store disinfected recycled syringe pgs.
 - D. synonymous with Clean or Cleanroom area.
11. The microbial risk level for preparing most radiopharmaceuticals is:
- A. medium.
 - B. immediate.
 - C. low.
 - D. high.
12. A designation of Low-Risk Level compounded sterile preparations (CSPs) applies to radiopharmaceutical units doses:
- A. with expiration times 24 hours or less.
 - B. compounded in a biological safety cabinet in an uncontrolled area.
 - C. compounded in a certified and properly sanitized ISO Class 5 laminar air flow workbench (LAFW) located in an ISO Class 8 area.
 - D. Containing preservatives. .

13. An investigation into the cause of a positive sterility test revealed the presence of Gram-positive cocci, which was most likely caused by:
- A. endospores.
 - B. humidity (>70%).
 - C. human touch.
 - D. water.
14. A disinfecting agent that will NOT sterilize a surface is:
- A. hydrogen peroxide.
 - B. benzalkonium chloride.
 - C. peracetic acid.
 - D. sodium hypochlorite.
15. The requirement for environmental monitoring includes which of the following:
- A. daily testing frequency.
 - B. glove-fingertips with dominant hand on contact plates.
 - C. daily glove-fingertip with settling plates.
 - D. an action limit of >3 cfu.
16. The USP suggested frequency for certifying laminar air flow workbenches is:
- A. semi-annually.
 - B. annually.
 - C. biannually.
 - D. only after a repair of the HEPA filter.
17. The greatest source of microbe-carrying particles is:
- A. personnel.
 - B. heat and air-conditioning system.
 - C. non-sterile gloves.
 - D. shoes and street clothes.
18. The term “critical site”, as in the context of USP Chapter <797>, includes which of the following:
- A. drain of a sink.
 - B. bevel tip of a needle.
 - C. face of a HEPA filter.
 - D. opening of an HVAC duct.
19. The best use of a solution of 70% IPA (isopropanol) in a cleanroom is as a/an:
- A. sanitizing agent.
 - B. antiseptic.
 - C. cleaning agent.
 - D. sterilant.

20. A simulated media fill for nuclear pharmacy requires:
- A. substitution of Fluid Thioglycollate Media (aka FTM) for pertechnetate.
 - B. incubation of media for 5 days at body temperature.
 - C. a procedure that simulates Tc 99m kit labeling, dilution and transfer.
 - D. a unique cleaning procedure.
21. The Garbing requirements of <797> for compounding Tc 99m kits do **not** require a:
- A. clean sleeves
 - B. dedicated lab coat
 - C. sterile mask.
 - D. sterile gloves
22. The best way to clean the septum of a vial is:
- A. spray with 70% IPA just prior to puncture.
 - B. swab with a felt tip saturated with 70% IPS.
 - C. immerse in a sterilant, such as hydrogen peroxide.
 - D. swab with an alcohol pad.
23. The primary engineering control (LAFW) should :
- A. run a minimum of 30 minutes before cleaning and use.
 - B. maintain a continuous air flow rate of 100 ft/sec \pm 20%..
 - C. be sanitized with a chlorine-based detergent after each shift.
 - D. Include pre-filters certified for particles 3 micron or larger.
24. Secondary engineering controls in a nuclear pharmacy may be needed to provide a classified environment that meets the standards for:
- A. ISO Class 1.
 - B. ISO Class 3
 - C. ISO Class 5
 - D. ISO Class 8
25. The organization or agency most likely to enforce USP Chapter <797> upon an individual nuclear pharmacy is:
- A. FDA through its aseptic processing guidelines.
 - B. a state Board of Pharmacy through its specific pharmacy regulations.
 - C. JCAHO through its accreditation service.
 - D. NABP through its model regulations for pharmacy.