BOARDS AND COMMISSIONS

Kentucky Board of Pharmacy

(Amendment)

201 KAR 2:076. Compounding.

RELATES TO: KRS 217.055(1)[(2)], 217.065(7), 315.020(1), 315.035(6), 315.0351, 315.191(1)(a), (g), 21 U.S.C. 353A

STATUTORY AUTHORITY: KRS 315.020(1), 315.035(6), 315.0351, 315.191(1)(a), (g)

NECESSITY, FUNCTION, AND CONFORMITY: KRS 315.020(1) requires the owner of a pharmacy who is not a pharmacist to place a pharmacist in charge of the owner's pharmacy. KRS 315.035(6) authorizes the board to promulgate administrative regulations to assure minimum standards of practice of compounding by pharmacies and pharmacists, and to assure the safety of all products provided to the citizens of the Commonwealth. KRS 315.191(1) authorizes to board to promulgate administrative regulations necessary to regulate and control all matters relating to pharmacists, pharmacist interns, pharmacy technicians, pharmacies, wholesale distributors, and manufacturers. This administrative regulation establishes the requirements for compounding non-sterile and sterile preparations, and the preparation, compounding, dispensing and repackaging of radiopharmaceuticals in accordance with 21 U.S.C. 353A.

Section 1. Definitions.

(1) “API” means active pharmaceutical ingredient.

(2) “Designated person” means one (1) or more individuals assigned to be responsible and accountable for the performance and operation of the facility and personnel as related to the preparation of compounded non-sterile or sterile preparations or the preparation, compounding, dispensing and repackaging of radiopharmaceuticals.

(3) “Essential copy of a commercially available drug product” is a compounded preparation in which:

(a) The compounded preparation has the same API as the commercially available drug product;

(b) The APIs have the same, similar, or an easily substitutable dosage strength; and

(c) The commercially available drug product can be used by the same route of administration as prescribed for the compounded preparations, unless a prescriber determines that there is a change, made for an identified individual patient, which produces, for that patient, a significant difference from the commercially available drug product.

(4) “Hazardous Drug” means any drug identified by the National Institute for Occupational Safety and Health with at least one of the following criteria:

(a) Carcinogenicity, teratogenicity or developmental toxicity;

(b) Reproductive toxicity in humans;

(c) Organ toxicity at low dose in humans or animals;

(d) Genotoxicity; or

(e) New drugs that mimic existing hazardous drugs in structure or toxicity.

(5) “USP” means United States Pharmacopeia.

Section 2 [~~1~~]. Policies and Procedures.

(1) A policy and procedure manual for non-sterile compounding shall be readily available at a pharmacy for inspection purposes.

(2) The policy and procedure[~~A copy of the~~] manual shall be made available to the board upon request.

(3) The manual shall be reviewed and revised on an annual basis.

Section 3 [~~2~~]. Standards.

(1) All non-sterile compounded preparations shall be compounded pursuant to [~~United States Pharmacopeia (USP)~~]USP 795[~~, unless specified portions submitted by a pharmacist have been waived by the board. Notwithstanding any USP guidance to the contrary~~].

(2) All sterile compounded preparations shall be compounded pursuant to USP 797[~~, unless specified portions submitted by a pharmacist have been waived by the board~~].

(3) All preparation, compounding, dispensing and repackaging of radiopharmaceuticals shall be pursuant to USP [~~United States Pharmacopeia (USP)~~] 825[~~, unless specified portions submitted by a pharmacist have been waived by the board~~].

(4) All non-sterile or sterile compounded preparations containing hazardous drugs shall be compounded pursuant to USP 800.

[~~(4) All written waiver requests submitted by a pharmacist shall be considered by the Board at its next regularly scheduled meeting.~~]

[~~(5) The board, upon a showing of good cause and in balancing the best interest of the public health, safety and welfare, may waive the requirement of any specified portion of USP 795, 797or 825.~~]

(5) Non-sterile and sterile preparations compounded for human use must:

(a) Comply with the standards of an applicable USP or National Formulary monograph; or

(b) Be compounded from a component of a human drug approved by the United States Food and Drug Administration (FDA); or

(c) Be compounded from a component that appears on the FDA's list of bulk drug substances that can be used in compounding.

(d) Not be essential copies of a commercially available drug product unless authorized by 21 U.S.C. 353(a).

Section 4 [~~3~~]. Designated Person.

(1) The designated person of a[~~A~~] facility that compounds non-sterile or sterile preparations or prepares, compounds, dispenses or repackages radiopharmaceuticals shall be [~~managed by a pharmacist-in-charge (PIC licensed to practice pharmacy in the Commonwealth and who is~~] knowledgeable in the specialized requirements[~~functions~~] of preparing and dispensing compounded [~~non-sterile and sterile~~] preparations[~~, including the principles of aseptic technique and quality assurance~~].

(2) The PIC shall be responsible for the appointment for any designated persons.[~~The PIC shall be responsible for the: purchasing, storage, compounding, repackaging, dispensing, of preparations, development and continuing review of all policies and procedures, training manuals, quality assurance programs, and participation in those aspects of the facility's patient care evaluation program relating to pharmaceutical material utilization and effectiveness.~~]

(3) The PIC shall be responsible to ensure any compounded preparation leaving the premises is shipped or delivered in a manner that maintains the integrity and stability of the preparation[~~may be assisted by additional pharmacy personnel adequately trained, to the satisfaction of the PIC, in this area of practice and for each product they will be compounding~~].

Section 5 [~~4~~]. Dispensing and Labeling.

(1) The pharmacist shall receive a written, electronic, facsimile, or verbal prescription, or medical order from a prescriber before dispensing any compounded, non-sterile or sterile preparation. These prescriptions or medical orders shall contain the following:

(a) Patient's name, and species if not human;

(b) Patient's address on controlled substances prescriptions or location (room number);

(c) Drug name and strength;

(d) Directions of use;

(e) Date;

(f) Authorized prescriber's name;

(g) Prescriber's address and DEA number, if applicable;

(h) Refill or end date instructions, if applicable; and

(i) Dispensing quantity, if applicable.

(2) A pharmacist dispensing compounded preparations for veterinary use must follow the order requirements of 201 KAR 2:311.[~~A pharmacy generated patient profile shall be maintained separate from the prescription file. The patient profile shall be maintained under the control of the PIC for a period of two (2) years following the last dispensing activity. In addition, a medication administration record (MAR) as part of the institutional~~

~~record shall be retained for a period of five (5) years from date of the patient's discharge from the facility, or in the case of a minor, three (3) years after the patient reaches the age of majority under state law, whichever is the longer. Supplemental records may also be employed as necessary. The patient profile shall contain:~~

~~(a) Patient's name;~~

~~(b) Name of compounded preparation dispensed;~~

~~(c) Date dispensed;~~

~~(d) Drug content and quantity; and~~

~~(e) Patient's directions.]~~

(3) Each compounded preparation dispensed to patients shall be labeled with the following information:

(a) Name, address, and telephone number of the licensed pharmacy, if preparation will leave the premises;

(b) Date;

(c) Identifying number;

(d) Patient's full name;

(e) Name of each drug, strength, and amount;

(f) Directions for use, including infusion rate;

(g) Required controlled substances transfer warning, where applicable;

(h) Beyond use date;

(i) Identity of dispensing pharmacist;

(j) Storage requirements, when applicable; and

(k) Auxiliary labels, when applicable.

(4) Verification of a compounded preparation shall be completed by a pharmacist after the preparation is compounded and prior to dispensing to the patient. Documentation of the verification shall include notation of each pharmacist who performs verification.

Section 6. Recordkeeping.

(1)[~~(4)~~] The PIC shall maintain access to and provide[~~submit, as appropriate, such~~] records and reports to the board or its agents upon request[~~as are required to ensure the patient's health, safety, and welfare~~]. Records shall be maintained and readily available for no less than five (5) years[~~, maintained for two (2) years at a facility not computerized, but for five (5) years at a facility utilizing computerized recordkeeping, and subject to inspection by the Board of Pharmacy or its agents~~].

(2) Records. Records[~~These~~] shall include the following:

(a) Prescriptions or medical orders or requests for compounded preparations[~~Patient profile~~];

(b) Purchase records;

(c) Verification records[~~Biennial controlled substances inventories~~]; and

(d) [~~Policy and procedures manual;~~

~~(e) Policies and procedures for hazardous wastes, if applicable;~~

~~(f) Quality assurance records;~~

~~(g)~~] Other records and reports as ~~may be~~ required by USP 795, 797, 800, and 825, state and federal law, and administrative regulations of the Kentucky Board of Pharmacy[~~KRS 217 or 315 and 201 KAR Chapter 2~~].

~~[(5) Information regarding individual patients shall be maintained in a manner to assure confidentiality of the patient's records. Release of this information shall be in accordance with federal and state laws.~~

~~(6) The PIC shall be responsible for the environmental control of all products shipped. Any compounded product that is frozen or requires refrigeration shall be shipped or delivered to a patient in appropriate temperature controlled delivery containers, if the product leaves the premises.~~

~~(7) The PIC shall be responsible for assuring that there is a system for the disposal of hazardous water in a manner that does not endanger the public health.~~

~~Section 5. Hazardous Drugs.~~

~~(1) All non-sterile preparations that contain hazardous substances shall be compounded pursuant to USP 795.~~

~~(2) All sterile compounded preparations that contain hazardous substances shall be compounded pursuant to USP 797.]~~

Section 7[~~6~~]. Violations.

Violation of any provision of this administrative regulation shall constitute unethical or unprofessional conduct in accordance with KRS 315.121.

Section 8. Waivers.

(1) All written waiver requests submitted by a pharmacy shall be considered by the Board at its next regularly scheduled meeting.

(2) The board, upon a showing of good cause and in balancing the best interest of the public health, safety and welfare, may waive the requirement of any specified portion of USP 795, 797, 800 or 825 or any provision of this regulation. Any waiver issued shall

identify with specificity the pharmacy to which is applies and the provisions of law for which the waiver is applied.

Section 9. Enforcement Discretion.

(1) The Board shall not enforce the provisions of this regulatory amendment requiring compliance with the 2022 revisions to USP Chapters USP 795 and 797 until January 1, 2026. Until January 1, 2026, the 2014 revision of USP 795 will be enforced and the 2008 revision of USP 797 will be enforced. USP 800 will not be enforced until January 1, 2026.

(2) The addition of flavoring to a commercially available drug shall not be considered non-sterile compounding, if the additive:

(a) Is non-expired, inert, nonallergenic, and produces no effect other than the instillation or modification of flavor; and

(b) Is not greater than five (5) percent of the drug product's total volume.

Section 10 [~~7~~]. Incorporation by Reference.

(1) The following material is incorporated by reference:

(a) "USP 795, Revision Bulletin, Official" November 1, 2022[~~January 1, 2014~~];

(b) "USP 797, Revision Bulletin, Official" November 1, 2022[~~June 1, 2008~~]; [~~and~~]

(c) "USP 825, Revision Bulletin, Official, Official" December 1, 2020[~~.~~]; and

(d) "USP 800, Revision Bulletin" December 1, 2020.

(2) This material may be inspected, copied, or obtained, subject to applicable copyrights law, at the Kentucky Board of Pharmacy, 125 Holmes Street, Suite 300, State Office Building Annex, Frankfort, Kentucky 40601, Monday through Friday, 8 a.m. through

4:30 p.m. This material is also available on the board's website at https://pharmacy.ky.gov/statutesandregulations/Pages/default.aspx.

June 7, 2023

CHRISTOPHER P. HARLOW,
Executive Director
Kentucky Board of Pharmacy

DATE

PUBLIC HEARING AND PUBLIC COMMENT PERIOD

A public hearing on this administrative regulation shall be held on August 30, 2023, at 10:00 a.m. Eastern Time via zoom teleconference. Individuals interested in being heard at this hearing shall notify this agency in writing by five workdays prior to the hearing, of their intent to attend. If no notification of intent to attend the hearing is received by that date, the hearing may be canceled. This hearing is open to the public. Any person who wishes to be heard will be given an opportunity to comment on the proposed administrative regulation. If you do not wish to be heard at the public hearing, you may submit written comments on the proposed administrative regulation. Written comments shall be accepted through August 31, 2023. Send written notification of intent to be heard at the public hearing or written comments on the proposed administrative regulation to the contact person.

Contact person: Christopher Harlow, Executive Director, Kentucky Board of Pharmacy, 125 Holmes Street, Suite 300, State Office Building Annex, Frankfort, Kentucky 40601, Phone (502) 564-7910, Fax (502) 696-3806, email Christopher.harlow@ky.gov.

REGULATORY IMPACT ANALYSIS
AND TIERING STATEMENT

201 KAR 2:076. Compounding.
Contact person: Christopher Harlow
Contact Phone No.: 502-564-7910
Contact email: Christopher.harlow@ky.gov

(1) Provide a brief summary of:

(a) What this administrative regulation does: This administrative regulation establishes the requirements for compounding non-sterile and sterile preparations, and the preparation, compounding, dispensing and repackaging of radiopharmaceuticals.

(b) The necessity of this administrative regulation: This administrative regulation is necessary to comply with federal regulation and to establish the requirements for compounding non-sterile and sterile preparations, and the preparation, compounding, dispensing and repackaging of radiopharmaceuticals.

(c) How this administrative regulation conforms to the content of the authorizing statutes: KRS 315.035(6) authorizes the Board of Pharmacy to promulgate administrative regulations to assure minimum standards of practice of compounding by pharmacies and pharmacists, and to assure the safety of all products provided to the citizens of the Commonwealth. This administrative regulation relates to the requirements for compounding non-sterile and sterile preparations, and the preparation, compounding, dispensing and repackaging of radiopharmaceuticals.

(d) How this administrative regulation currently assists or will assist in the effective administration of the statutes: This administrative regulation establishes the requirements for compounding non-sterile and sterile preparations, and the preparation, compounding, dispensing and repackaging of radiopharmaceuticals. This administrative regulation assures minimum standards of practice of compounding by pharmacies and pharmacists are established and assures the safety of all products provided to citizens of the Commonwealth.

(2) If this is an amendment to an existing administrative regulation, provide a brief summary of:

(a) How the amendment will change this existing administrative regulation: This amendment conforms to the updated USP chapters, which are required under federal regulation.

(b) The necessity of the amendment to this administrative regulation: This amendment is necessary to comply with federal regulation.

(c) How the amendment conforms to the content of the authorizing statutes: KRS 315.035(6) authorizes the Board of Pharmacy to promulgate administrative

regulations to assure minimum standards of practice of compounding by pharmacies and pharmacists, and to assure the safety of all products provided to the citizens of the Commonwealth. This amendment assures minimum standards of practice of compounding by pharmacies and pharmacists are established.

(d) How the amendment will assist in the effective administration of the statutes: This administrative regulation assures minimum standards of practice of compounding by pharmacies and pharmacists are established.

(3) List the type and number of individuals, businesses, organizations, or state and local government affected by this administrative regulation: This administrative regulation impacts pharmacists and pharmacies.

(4) Provide an analysis of how the entities identified in question (3) will be impacted by either the implementation of this administrative regulation, if new, or by the change, if it is an amendment, including:

(a) List the actions that each of the regulated entities identified in question (3) will have to take to comply with this administrative regulation or amendment: This administrative regulation provides pharmacists and pharmacies with the requirements for compounding non-sterile and sterile preparations, and the preparation, compounding, dispensing and repackaging of radiopharmaceuticals. If engaging in the practice of compounding, pharmacists and pharmacies shall meet the requirements set forth in this administrative regulation.

(b) In complying with this administrative regulation or amendment, how much will it cost each of the entities identified in question (3): Pharmacists and pharmacies will incur no costs in complying with this administrative regulation.

(c) As a result of compliance, what benefits will accrue to the entities identified in question (3). The ability to engage in the practice of compounding in a manner that assures the safety of all products provided to the citizens of the Commonwealth.

(5) Provide an estimate of how much it will cost to implement this administrative regulation:

(a) Initially: No cost to the administrative body.

(b) On a continuing basis: No cost to the administrative body.

(6) What is the source of the funding to be used for the implementation and enforcement of this administrative regulation: The Board of Pharmacy will inspect pharmacies and pharmacist practice to ensure compliance with this administrative regulation. The Board of Pharmacy already employs inspectors, and this regulation will not increase any cost of enforcement for the Board of Pharmacy.

(7) Provide an assessment of whether an increase in fees or funding will be necessary to implement this administrative regulation, if new, or by the change if it is an amendment: There will be no increase in fees or funding necessary to implement this regulation.

(8) State whether or not this administrative regulation establishes any fees or directly or indirectly increases any fees: This administrative regulation does not establish any fees directly or indirectly.

(9) TIERING: Is tiering applied? (Explain why tiering was or was not used)
Tiering is not applied, as this administrative regulation establishes the minimum standards the requirements for compounding non-sterile and sterile preparations, and the preparation, compounding, dispensing and repackaging of radiopharmaceuticals, it simply provides the requirements for the practice of compounding.

FISCAL NOTE

201 KAR 2:076. Compounding.
Contact person: Christopher Harlow
Contact Phone No.: 502-564-7910
Contact email: Christopher.harlow@ky.gov

(1) What units, parts, or divisions of state or local government (including cities, counties, fire departments, or school districts) will be impacted by this administrative regulation? There will be no impact on local or state government outside of the Board of Pharmacy's enforcement of the regulation.

(2) Identify each state or federal statute or federal regulation that requires or authorizes the action taken by the administrative regulation. KRS 315.020(1), 315.035(6), 315.0351, 315.191(1)(a) and (g), and 21 U.S.C 353(a).

(3) Estimate the effect of this administrative regulation on the expenditures and revenues of a state or local government agency (including cities, counties, fire departments, or school districts) for the first full year the administrative regulation is to be in effect. There will be no effect on the expenditures and revenue of a state or local government agency.

(a) How much revenue will this administrative regulation generate for the state or local government (including cities, counties, fire departments, or school districts) for the first year? This administrative regulation will not generate any revenue for the state or local government.

(b) How much revenue will this administrative regulation generate for the state or local government (including cities, counties, fire departments, or school districts) for subsequent years? This administrative regulation will not generate revenue.

(c) How much will it cost to administer this program for the first year? There will be no cost to administer this administrative regulation. The cost of educating pharmacists and having pharmacist inspectors provide guidance is built into the employment cost for those staff members.

(d) How much will it cost to administer this program for subsequent years? This administrative regulation will not generate costs.

Note: If specific dollar estimates cannot be determined, provide a brief narrative to explain this fiscal impact of the administrative regulation.

Revenues (+/-): 0

Expenditures (+-): 0
Other Explanation: This regulation will not create additional costs for the agency.

(4) Estimate the effect of this administrative regulation on the expenditures and cost savings of regulated entities for the first full year the administrative regulation is to be in effect? There will be no impact on the expenditures or cost savings of the regulated entities. Pharmacies will have to come into compliance with USP 795, 797 and 800 respectively. This can take significant time and expenditure, and that is why the Board has built in a period of enforcement discretion.

(a) How much cost savings will this administrative regulation generate for the regulated entities for the first year? There will be no impact on the expenditures or cost savings of regulated entities.

(b) How much cost savings will this administrative regulation generate for the regulated entities for subsequent years? There will be no impact on the expenditures or cost savings of regulated entities.

(c) How much will it cost the regulated entities for the first year? Regulated entities that are not in compliance with the federal standard will need to come into compliance, and installing the appropriate mechanisms to be in compliance could cost regulated entities a significant sum, and that is why the Board is building in a period of enforcement discretion. During that period, the state will not enforce to the new standard, but the FDA could still come in and they will be inspecting to the new standard despite the state's exercise of enforcement discretion.

(d) How much will it cost the regulated entities for subsequent years? There will be no impact on the expenditures or cost savings of regulated entities. Once regulated entities come into compliance, there will be no further cost for regulated entities.

Note: If specific dollar estimates cannot be determined, provide a brief narrative to explain the fiscal impact of the administrative regulation.

Cost Savings (+/-): 0

Expenditures (+/-): not uniform, cannot be quantified.

Other Explanation: This regulation does require pharmacies to come into compliance with USP 795, 797 and 800, depending on the type of compounding they are performing. It is our understanding that for some pharmacies, this will be costly. This is why the Board does not plan on enforcing the standards until 2026.

(5) Explain whether this administrative regulation will have a major economic impact, as defined below. "Major economic impact" means an overall negative or adverse economic impact from an administrative regulation of five hundred thousand dollars ($500,000) or more on state or local government or regulated entities, in aggregate, as determined by the promulgating administrative bodies. [KRS 13A.010(13)] This administrative regulation will not have a major economic impact.

FEDERAL MANDATE ANALYSIS COMPARISON

201 KAR 2:076. Compounding.
Contact person: Christopher Harlow
Contact Phone No.: 502-564-7910
Contact email: Christopher.harlow@ky.gov

(1) Federal statute or regulation constituting the federal mandate. 21 U.S.C. 353A.

(2) State compliance standards. 21 U.S.C. 353A is section 503A of the federal Food, Drug and Cosmetic Act. This section of law creates federal floor requirements for pharmacies that are compounding drugs. This regulatory amendment ensures congruence with 21 U.S.C. 353A.

(3) Minimum or uniform standards contained in the federal mandate. 21 U.S.C. 353A requires non-sterile compounding to follow USP Chapter 795, sterile compounding to follow USP Chapter 797 and hazardous drug compounding to follow USP 800. Moreover, 21 U.S.C. 353A prohibits the compounding of a commercially available drug unless certain requirements are met. This amendment includes the same regulatory language as 21 U.S.C. 353A.

(4) Will this administrative regulation impose stricter requirements, or additional or different responsibilities or requirements, than those required by the federal mandate? No, this regulatory amendment only imposes the floor requirement of the federal rule.

(5) Justification for the imposition of the stricter standard, or additional or different responsibilities or requirements. Not applicable because we have only adopted the federal minimum standard.

SUMMARY OF MATERIAL INCORPORATED BY REFERENCE

(1) "USP 795, Revision Bulletin, Official" November 1, 2022 is the 11-page document incorporated by reference as the federal standard required for non-sterile compounding.
(2) "USP 797, Revision Bulletin, Official" November 1, 2022 is the 33-page document incorporated by reference as the federal standard for sterile compounding.
(3) "USP 825, Revision Bulletin, Official, Official" December 1, 2020 is the 18-page document incorporated by reference as the federal standard for radiopharmaceutical compounding; and
(4) "USP 800, Revision Bulletin" December 1, 2020 is the 28-page document incorporated by reference as the federal standard for hazardous waste compounding.

SUMMARY OF CHANGES TO MATERIAL INCORPORATED BY REFERENCE

On November 1, 2022, Untied States Pharmacopeia (USP) published revisions to their pharmaceutical compounding standards chapter 795 (nonsterile preparations) and 797 (sterile preparations) with an implementation date of November 1, 2023 for both. The revisions for chapter 795 eliminated the categories for non-sterile compounding, provided clearer documentation requirements, introduced using water activity (a_w) to determine beyond use dates and outlined quality assurance, quality control and garbing requirements. The revisions for chapter 797 included clearer documentation requirements, training requirements as well as environmental control requirements, changed the categories for sterile compounding, updated beyond use dates, and outlined quality assurance, quality control and garbing requirements.

⟨795⟩ PHARMACEUTICAL COMPOUNDING—NONSTERILE PREPARATIONS

Change to read:

▲1. INTRODUCTION AND SCOPE

This chapter describes the minimum standards to be followed for the preparation of compounded nonsterile preparations (CNSPs) for humans and animals. For purposes of this chapter, nonsterile compounding is defined as combining, admixing, diluting, pooling, reconstituting other than as provided in the manufacturer's labeling, or otherwise altering a drug product or bulk drug substance to create a nonsterile preparation.

The requirements in this chapter must be followed to minimize harm, including death, to human and animal patients that could result from 1) excessive microbial contamination, 2) variability from the intended strength of correct ingredients (e.g., ±10% of the labeled strength), 3) physical and chemical incompatibilities, 4) chemical and physical contaminants, and/or 5) use of ingredients of inappropriate quality.

Handling of nonsterile hazardous drugs (HDs) must additionally comply with *Hazardous Drugs—Handling in Healthcare Settings* ⟨800⟩.

1.1 Scope

1.1.1 CNSPs subject to the requirements in this chapter: CNSPs that must comply with this chapter include but are not limited to the following dosage forms:

- Solid oral preparations
- Liquid oral preparations
- Rectal preparations
- Vaginal preparations
- Topical preparations (i.e., creams, gels, and ointments)
- Nasal and sinus preparations intended for local application (i.e., nasal sprays and nasal irrigation)
- Otic preparations (excluding use in perforated eardrums)

1.1.2 Practices not subject to the requirements in this chapter: The following practices are not considered compounding and are not required to meet the requirements of this chapter. Handling of nonsterile HDs should additionally comply with ⟨800⟩. Refer to facility SOPs for additional safe practices (e.g., labeling).

- *Nonsterile radiopharmaceuticals:* Compounding of nonsterile radiopharmaceuticals is subject to the requirements in *Radiopharmaceuticals—Preparation, Compounding, Dispensing, and Repackaging* ⟨825⟩.
- *Reconstitution:* Reconstitution of a conventionally manufactured nonsterile product in accordance with the directions contained in the manufacturer approved labeling
- *Repackaging:* Repackaging of conventionally manufactured drug products (see *Good Repackaging Practices* ⟨1178⟩ for recommendations)
- *Splitting tablets:* Breaking or cutting a tablet into smaller portions
- *Administration:* Preparation of a single dose for a single patient when administration will begin within 4 h. This includes crushing a tablet(s) or opening a capsule(s) to mix with food or liquids to facilitate patient dosing.

1.1.3 Personnel and settings affected: This chapter applies to all persons who prepare CNSPs and all places where CNSPs are prepared. This includes but is not limited to pharmacists, technicians, nurses, physicians, veterinarians, dentists, naturopaths, and chiropractors in all places including but not limited to pharmacies, hospitals and other healthcare institutions, patient treatment sites, and physicians' or veterinarians' practice sites.

The compounding facility's leadership and all personnel involved in preparing, storing, packaging, dispensing, and transporting CNSPs are responsible for 1) ensuring that the applicable practices and quality standards in this chapter are continually and consistently applied to their operations, and 2) proactively identifying and remedying potential problems within their operations. Personnel engaged in the compounding and dispensing of CNSPs must also comply with laws and regulations of the applicable regulatory jurisdiction.

1.1.4 Oversight by designated person(s): The compounding facility must designate one or more individuals to be responsible and accountable for the performance and operation of the facility and personnel for the preparation of CNSPs. The responsibilities of the designated person(s) include but are not limited to:

- Overseeing a training program to ensure competency of personnel involved in compounding, handling, and preparing CNSPs
- Selecting components
- Monitoring and observing compounding activities and taking immediate corrective action if deficient practices are observed
- Ensuring that standard operating procedures (SOPs) are fully implemented. The designated person(s) must ensure that follow-up is carried out if problems, deviations, or errors are identified
- Establishing, monitoring, and documenting procedures for the handling and storage of CNSPs and/or components of CNSPs

The designated person(s) must be identified in the facility's SOPs. If the compounding facility has only one person responsible for all compounding in the facility, then that person is the designated person.

2. PERSONNEL TRAINING AND EVALUATION

All personnel who compound or have direct oversight of compounding CNSPs must be initially trained and qualified by demonstrating knowledge and competency according to the requirements in this section (*2. Personnel Training and Evaluation*) before being allowed to perform their job functions independently.

Designated person(s) are responsible for creating and implementing a training program that describes the required training, the frequency of training, and the process for evaluating the competency of personnel. This program must equip personnel with knowledge and training in the required skills necessary to perform their assigned tasks. Personnel who compound or have direct oversight of compounding personnel must complete training initially and at least every 12 months in appropriate compounding principles and practices as described in this section. Other personnel, who do not compound and only perform functions such as in-process checks, final verification, or dispensing of CNSPs, must undergo training as required by the facility's SOPs.

Training and competency of personnel must be documented as described in *14. Documentation*.

Before beginning to compound CNSPs independently or have direct oversight of compounding personnel, personnel must complete training and be able to demonstrate knowledge of principles and competency of skills for performing nonsterile manipulations as applicable to their assigned tasks. Knowledge and competency must be demonstrated initially and at least every 12 months in at least the following core competencies:

- Hand hygiene
- Garbing
- Cleaning and sanitizing
- Handling and transporting components and CNSPs
- Measuring and mixing
- Proper use of equipment and devices selected to compound CNSPs
- Documentation of the compounding process (e.g., *7. Master Formulation and Compounding Records*)

Steps in the training procedure must include the following:

- Understand the requirements in this chapter
- Understand and interpret safety data sheets (SDSs) and, if applicable, certificates of analysis (COA)
- Read and understand procedures related to their compounding duties

Training and observation may be performed by the designated person(s) or an assigned trainer. Personnel must be observed and guided throughout the training process. The personnel will then be expected to repeat the procedures independently while under the direct supervision of the designated person(s) and/or assigned trainer. Personnel will be permitted to perform the procedure without direct supervision only after independently demonstrating understanding and competency. Upon completion of the training program, the designated person(s) and/or assigned trainer must document that personnel have been trained and successfully completed competency assessments (see *14. Documentation*).

In addition to the initial and annual competency training and evaluation described in this section, the designated person(s) should monitor and observe compounding activities and must take immediate corrective action if deficient practices are observed. Facility SOPs must describe procedures for monitoring and observing compounding activities and personnel.

If the facility has only one person in the compounding operation, that person must document that they have obtained training and demonstrated competency, and they must comply with the other requirements of this chapter.

3. PERSONAL HYGIENE AND GARBING

Individuals entering the compounding area must maintain appropriate personal hygiene. Individuals must evaluate whether they have a personal risk of potentially contaminating the compounding environment and CNSP (e.g., personnel with rashes, recent tattoos, oozing sores, conjunctivitis, or active respiratory infection). Individuals must report these conditions to the designated person(s). Because of the risk of contaminating the CNSP and the environment, the designated person(s) is responsible for evaluating whether these individuals should be excluded from working in compounding areas until their conditions have resolved.

3.1 Personnel Preparation

Personnel engaged in compounding must maintain appropriate hand hygiene and maintain appropriate cleanliness required for the type of compounding performed.

Before entering the compounding area, compounding personnel must remove any items that are not easily cleanable and that might interfere with garbing. At a minimum, personnel must:

- Remove personal outer garments (e.g., bandanas, coats, hats, and jackets)
- Remove all hand, wrist, and other exposed jewelry, including piercings that could interfere with the effectiveness of garbing or hand hygiene (e.g., watches or rings that may tear gloves)
- Remove earbuds or headphones

The designated person(s) may permit accommodations provided that the quality of the environment and CNSP will not be affected. All accommodations should be documented.

3.2 Hand Hygiene

Personnel must perform procedures necessary for appropriate hand hygiene when entering the compounding area to compound as described in *Box 1*.

The use of alcohol-based hand rub alone is not sufficient.

Box 1. Hand Hygiene Procedures

- Wash hands with soap and water for at least 30 s
- Dry hands completely with disposable towels or wipers
- Don gloves

To minimize the risk of cross contaminating other CNSPs and contaminating other objects (e.g., pens and keyboards), gloves should be wiped or replaced before beginning a CNSP that has different components.

All gloves must be inspected for holes, punctures, or tears and must be replaced immediately if such defects are detected.

3.3 Garb and Glove Requirements

Gloves must be worn for all compounding activities. Other garb (e.g., shoe covers, head or hair covers, facial hair covers, face masks, and gowns) must be appropriate for the type of compounding performed and should be worn as needed for the protection of personnel from chemical exposures and for prevention of CNSP contamination. Garbing requirements and frequency of changing garb must be determined by the facility and documented in the facility's SOPs.

Garb must be replaced immediately if it becomes visibly soiled or if its integrity is compromised. All gloves must be inspected for holes, punctures, or tears and must be replaced immediately if such defects are detected. Garb must be stored in a manner that minimizes contamination (e.g., away from sinks to avoid splashing).

Garb should be removed when leaving the compounding area. When personnel exit the compounding area, garb, except for gowns, should be discarded. Disposable garb must not be laundered. If gowns are worn, they may be reused if not damaged or soiled. If gowns are to be reused, they must remain in the compounding area, and should only be reused during the same shift. The facility's SOPs must describe cleaning and sanitization procedures for reusing goggles, respirators, and other reusable equipment.

If compounding an HD, appropriate personal protective equipment (PPE) must be worn and disposed of in accordance with ⟨800⟩.

4. BUILDINGS AND FACILITIES

4.1 Compounding Area

An area must be designated for nonsterile compounding. The method of designation must be described in the facility's SOPs. Other activities must not be occurring in the compounding area at the same time as compounding. The compounding area must be well lit and must be maintained in a clean, orderly, sanitary condition and in a good state of repair. There should not be carpet in the compounding area.

The compounding area must provide for the orderly placement of equipment and materials to prevent mix-ups among components, containers, labels, in-process materials, and finished CNSPs. The area should be designed, arranged, and used in a way that minimizes cross contamination from noncompounding areas.

4.2 Storage Area

Compounding personnel must monitor temperatures in the storage area(s) either manually at least once daily on days that the facility is open, or continuously with a temperature recording device to ensure the temperature remains within the appropriate range for the CNSPs and components. The results of the temperature readings must be documented on a temperature log or stored in the continuous temperature recording device and must be retrievable. All temperature monitoring equipment must be calibrated or verified for accuracy as recommended by the manufacturer or every 12 months if not specified by the manufacturer.

The compounding facility must adhere to SOPs to detect and reduce the risk of temperature excursions within the storage area(s).

When it is known that a CNSP or component has been exposed to temperatures either below or above the storage temperature limits for the CNSP or component, personnel must determine whether the CNSP or component integrity or quality has been compromised, and, if so, the CNSP or component must be discarded.

All CNSPs, components, equipment, and containers must be stored off the floor in a manner that prevents contamination and permits inspection and cleaning of the storage area(s).

4.3 Water Sources

A source of hot and cold water and an easily accessible sink must be available. The sink must be emptied of all items unrelated to compounding and must be cleaned if visibly soiled before being used to clean any equipment used in nonsterile compounding. The plumbing system must be free of defects that may contribute to the contamination of any CNSP. *Purified Water* (see *Water for Pharmaceutical Purposes* ⟨1231⟩*, 3.1.1 Purified Water*), distilled water, or reverse osmosis water should be used for rinsing equipment and utensils.

5. CLEANING AND SANITIZING

Cleaning and sanitizing the surfaces in the nonsterile compounding area(s) must occur on a regular basis at the minimum frequencies specified in *Table 1* or, if compounding is not performed daily, cleaning and sanitizing must be completed before initiating compounding. Cleaning and sanitizing must be repeated when spills occur and when surfaces are visibly soiled. Applicable cleaning and sanitizing must be documented daily on days when compounding occurs.

Surfaces should be resistant to damage by cleaning and sanitizing agents. Floors in the compounding area should be easily cleanable and should not be porous or particle generating.

Cleaning and sanitizing agents must be selected and used with consideration of compatibilities, effectiveness, and minimal potential to leave residues.

If cleaning and sanitizing are performed as separate steps, cleaning must be performed first.

Table 1. Minimum Frequency for Cleaning and Sanitizing in Nonsterile Compounding Area(s)—Surfaces

Site	Minimum Frequency
Work surfaces	• At the beginning and end of each shift on days when compounding occurs, after spills, and when surface contamination (e.g., from splashes) is known or suspected • Between compounding CNSPs with different components
Floors	• Daily on days when compounding occurs, after spills, and when surface contamination (e.g., from splashes) is known or suspected
Walls	• When visibly soiled, after spills, and when surface contamination (e.g., from splashes) is known or suspected
Ceilings	• When visibly soiled and when surface contamination (e.g., from splashes) is known or suspected

Table 1. Minimum Frequency for Cleaning and Sanitizing in Nonsterile Compounding Area(s)—Surfaces *(continued)*

Storage shelving	• Every 3 months, after spills, and when surface contamination (e.g., from splashes) is known or suspected

6. EQUIPMENT AND COMPONENTS

6.1 Equipment

The equipment and components used for compounding a CNSP must be suitable for the specific compounding process.

Equipment surfaces that contact components must not be reactive, additive, or sorptive, and must not alter the quality of the CNSP. Disposable or dedicated equipment may be used to reduce the chance of bioburden and cross contamination.

Equipment must be stored in a manner that minimizes the risk of contamination and must be located to facilitate equipment use, maintenance, and cleaning. Equipment and devices used in the compounding or testing of compounded preparations must be inspected prior to use and, if appropriate, verified for accuracy as recommended by the manufacturer at the frequency recommended by the manufacturer or at least every 12 months, whichever is more frequent. After compounding, the equipment must be cleaned to prevent cross contamination of the next preparation.

Weighing, measuring, or otherwise manipulating components that could generate airborne chemical particles (e.g., active pharmaceutical ingredients [APIs], added substances, and conventionally manufactured products) must be evaluated to determine if these activities must be performed in a closed-system processing device to reduce the potential exposure to personnel or contamination of the facility or CNSPs. Examples of closed-system processing devices include containment ventilated enclosures (CVEs), biological safety cabinets (BSCs), and single-use containment glove bags. The process evaluation must be carried out in accordance with the facility's SOPs, and the assessment must be documented.

If a CVE or BSC is used, it must be certified at least every 12 months according to manufacturer specifications or other laws and regulations of the applicable regulatory jurisdiction.

If a BSC, CVE, or other nondisposable device is used, it must be cleaned as described in *Table 2*.

Table 2. Minimum Frequency for Cleaning and Sanitizing in Nonsterile Compounding Area(s)—Equipment

Site	Minimum Frequency
CVE	• At the beginning and end of each shift on days when compounding occurs, after spills, and when surface contamination (e.g., from splashes) is known or suspected • Clean and sanitize the horizontal work surface of the CVE between compounding CNSPs with different components
BSC	• At the beginning and end of each shift on days when compounding occurs, after spills, and when surface contamination (e.g., from splashes) is known or suspected • Clean and sanitize the horizontal work surface of the BSC between compounding CNSPs with different components • Clean and sanitize under the work surface at least monthly
Other devices and equipment used in compounding operations	• Before first use and thereafter in accordance with the manufacturer's recommendations • If no recommendation is available, between compounding CNSPs with different components

6.2 Components

The compounding facility must have written SOPs for the selection and inventory control of all components from receipt to use in a CNSP.

SDSs must be readily accessible to all personnel working with components located in the compounding facility. Personnel must be instructed on how to retrieve and interpret needed information.

6.2.1 Component selection: Designated person(s) must be responsible for selecting components to be used in compounding.

APIs:

- Must comply with the criteria in the *USP–NF* monograph, if one exists
- Must have a COA that includes specifications (e.g., compendial requirements for quality) and test results for the component that show the API meets expected quality
- In the United States, must be manufactured by an FDA-registered facility
- Outside of the United States, must comply with the laws and regulations of the applicable regulatory jurisdiction

All components other than APIs:

- Should be accompanied by a COA that verifies that the component meets the criteria in the *USP–NF* monograph, if one exists, and any additional specifications for the component
- In the United States, should be manufactured by an FDA-registered facility (If a component cannot be obtained from an FDA-registered facility, the designated person(s) must select a component that is suitable for the intended use.)
- Outside of the United States, must comply with the laws and regulations of the applicable regulatory jurisdiction

Water:

- *Purified Water* or better quality, e.g., *Sterile Water for Irrigation*, must be used for compounding nonsterile drug preparations when formulations indicate the inclusion of water

6.2.2 Component receipt: Upon receipt of components other than conventionally manufactured products, the COA must be reviewed to ensure that the component has met the acceptance criteria in an appropriate *USP–NF* monograph, if one exists. The following information must be documented (see *14. Documentation*) according to the facility's SOPs:

receipt date, quantity received, supplier name, lot number, expiration date, and results of any in-house or third-party testing performed.

For all components that lack a vendor expiration date, the date of receipt by the compounding facility must be clearly and indelibly marked on each packaging system. Packaging systems of components (i.e., API and added substances) that lack a vendor's expiration date must not be used by the compounding facility after 3 years from the date of receipt. A shorter expiration date must be assigned according to *Pharmaceutical Compounding—Sterile Preparations* ⟨797⟩*, 9.3.2 Component receipt* if the same component container is also used in sterile compounding or if the ingredient is known to be susceptible to degradation.

Any component found to be of unacceptable quality must be promptly rejected, clearly labeled as rejected, and segregated from active stock to prevent use before appropriate disposal. Any other lots of that component from the same vendor must be examined to determine whether the other lots have the same defect.

6.2.3 Component evaluation before use: Before use, compounding personnel must visually re-inspect all components. Each packaging system must be inspected to detect any container breakage, looseness of the cap or closure, or deviation from the expected appearance or texture of the contents that might have occurred during storage.

Compounding personnel must ascertain before use that components are of the correct identity based on the labeling and have been stored under required conditions in the facility.

If the identity, strength, purity, and quality of components intended for preparation of CNSPs cannot be verified (e.g., containers with damaged or incomplete labeling), the components must be immediately rejected. Any component found to be of unacceptable quality must be promptly rejected, clearly labeled as rejected, and segregated from active stock to prevent use before appropriate disposal.

6.2.4 Component handling: All components must be handled in accordance with the manufacturer's instructions or per laws and regulations of the applicable regulatory jurisdiction. The handling must minimize the risk of contamination, mix-ups, and deterioration (e.g., loss of identity, strength, purity, or quality). For each use, the lot must be examined for evidence of deterioration and other aspects of unacceptable quality. Once removed from the original container, any component not used in compounding (e.g., excess after weighing) should be discarded and not returned to the original container to minimize the risk of contaminating the original container.

6.2.5 Component spill and disposal: The facility must maintain current chemical hazard and disposal information (e.g., SDSs). Such information must be made accessible to compounding personnel.

The management and documentation of nonhazardous component spills and disposal must be described in the facility's SOPs.

The facility must have a readily accessible spill kit in the compounding area.

All personnel who may be required to remediate a spill must receive training in spill management of chemicals used and stored at the compounding facility. Training must be conducted at least every 12 months and documented for all personnel who may be required to clean up a spill.

Waste of any component must be disposed of in accordance with laws and regulations of the applicable regulatory jurisdiction. For information on the handling of HDs, see ⟨800⟩.

7. MASTER FORMULATION AND COMPOUNDING RECORDS

7.1 Creating Master Formulation Records

A master formulation record (MFR) is a detailed record of procedures that describes how the CNSP is to be prepared. An MFR must be created for each unique formulation of a CNSP. CNSPs are prepared according to the MFR, and the details of each preparation are documented on a compounding record (see *7.2 Creating Compounding Records*). Any changes or alterations to the MFR must be approved and documented according to the facility's SOP. See *Box 2* for information that must be included in an MFR.

Box 2. Master Formulation Record

An MFR must include at least the following information:

- Name, strength or activity, and dosage form of the CNSP
- Identities and amounts of all components; if applicable, relevant characteristics of components (e.g., particle size, salt form, purity grade, solubility)
- Container closure system(s)
- Complete instructions for preparing the CNSP including equipment, supplies, and description of compounding steps
- Physical description of the final CNSP
- Beyond-use date (BUD) and storage requirements
- Reference source to support the assigned BUD
- If applicable, calculations to determine and verify quantities and/or concentrations of components and strength or activity of the API(s)
- Labeling requirements (e.g., shake well)
- Quality control (QC) procedures (e.g., pH testing, visual inspection) and expected results
- Other information needed to describe the compounding process and ensure repeatability (e.g., adjusting pH, temperature)

7.2 Creating Compounding Records

A compounding record (CR) documents the compounding of each CNSP. A CR must be created for all CNSPs. Each CR must be reviewed for completeness before the CNSP is released. The name or other unique identifier of the person completing the review and the date of the review must be documented on the CR. The CR must permit traceability of all components in the case of a recall or known quality issue. The MFR can be used as the basis for preparing the CR. For example, a duplicate can be made of the MFR with blank fields for recording the information necessary to complete the CR. See *Box 3* for information that must be included in a CR.

Box 3. Compounding Record

A CR must include at least the following information:

- Name, strength or activity, and dosage form of the CNSP
- Date—or date and time—of preparation of the CNSP
- Assigned internal identification number (e.g., prescription, order, or lot number)
- A method to identify the individuals involved in the compounding process and individuals verifying the final CNSP
- Name, vendor or manufacturer, lot number, and expiration date of each component
- Weight or measurement of each component
- Total quantity of the CNSP compounded
- Assigned beyond-use date (BUD) and storage requirements
- If applicable, calculations to determine and verify quantities and/or concentrations of components and strength or activity of the API(s)
- Physical description of the final CNSP
- Results of quality control procedures (e.g., pH testing and visual inspection)
- MFR reference for the CNSP

8. RELEASE INSPECTIONS AND TESTING

All release inspections must be included in the facility's documentation (see *7. Master Formulation and Compounding Records* and *11. SOPs*). All checks, inspections, and any other required tests to ensure the quality of the CNSP must be detailed in the facility's MFR.

8.1 Visual Inspection

At the completion of compounding, before releasing and dispensing, the CNSP must be visually inspected to determine whether the physical appearance of the CNSP is as expected (e.g., color, texture, physical uniformity). Some CNSPs, as noted in their MFR, also must be visually checked for certain characteristics (e.g., emulsions must be checked for phase separation). The CNSP must be visually inspected to confirm that the CNSP and its labeling match the CR and the prescription or medication order. The inspection also must include a visual inspection of container closure integrity (e.g., checking for leakage, cracks in the container, or improper seals).

When a CNSP will not be released or dispensed on the day of preparation, a visual inspection must be conducted immediately before it is released or dispensed to make sure that the CNSP does not exhibit any defects (e.g., leakage) that could develop during storage. Any CNSP found to be of unacceptable quality (e.g., observed defects) must be promptly rejected, clearly labeled as rejected, and segregated from active stock to prevent use before appropriate disposal.

9. LABELING

Every CNSP must be labeled with appropriate, legible identifying information to prevent errors during storage, dispensing, and use. The term *labeling* designates all labels and other written, printed, or graphic matter on the immediate container or on or inside any packaging system or wrapper in which the article is enclosed, except any outer shipping container. The term *label* designates the part of the labeling on the immediate container. (See *Labeling* ⟨*7*⟩.)

All labeling must be in compliance with laws and regulations of the applicable regulatory jurisdiction.

The label on each container of the prepared CNSP must, at a minimum, display prominently and legibly the following information:

- Assigned internal identification number (e.g., barcode, prescription, order, or lot number)
- Active ingredient(s), and their amount(s), activity(ies), or concentration(s)
- Storage conditions if other than controlled room temperature
- BUD
- Dosage form
- Total amount or volume if it is not obvious from the container

The labeling on the dispensed CNSP should display the following information:

- Route of administration
- Indication that the preparation is compounded
- Any applicable special handling instructions
- Any applicable warning statements
- Compounding facility name, and contact information if the CNSP is to be sent outside of the facility or healthcare system in which it was compounded

Labeling procedures must be followed as described in the facility's SOPs to prevent labeling errors and CNSP mix-ups.

The label of the CNSP must be verified to ensure that it conforms with the following:

1. Prescription or medication order;
2. MFR (see *7.1 Creating Master Formulation Records*); and
3. CR (see *7.2 Creating Compounding Records*).

10. ESTABLISHING BEYOND-USE DATES

10.1 Terminology

Each CNSP label must state the date, or the hour and date, beyond which the preparation cannot be used and must be discarded (i.e., the BUD). BUDs for CNSPs are calculated in terms of hours, days, or months.

BUDs and expiration dates are not the same. An expiration date identifies the time during which a conventionally manufactured product, API, or added substance can be expected to meet the requirements of a compendial monograph, if one exists, or maintain expected quality, provided it is kept under the prescribed storage conditions. The expiration date limits the time during which a conventionally manufactured product, API, or added substance may be dispensed or used (see ⟨*7*⟩, *Labels and Labeling for Products in Other Categories, Expiration Date and Beyond-Use Date*).

10.2 Parameters to Consider in Establishing a BUD

BUDs for CNSPs should be established conservatively to ensure that the preparation maintains its required characteristics to minimize the risk of contamination or degradation.

When establishing a BUD for a CNSP, compounders must consider parameters that may affect quality, including but not limited to the following:

- Chemical and physical stability properties of the API and any added substances in the preparation (e.g., if the API and added substances in the preparation are known to rapidly degrade over time and/or under certain storage conditions, reduce the strength of the preparation, or produce harmful impurities)
- Compatibility of the container closure system with the finished preparation (e.g., leachables, interactions, adsorption, and storage conditions)
- Degradation of the container closure system, which can lead to a reduction in integrity of the CNSP
- Potential for microbial proliferation in the CNSP
- Significant deviations from essential compounding steps and procedures; changes to essential compounding steps may have an impact on the stability of the formulation

10.3 Establishing a BUD for a CNSP

The BUDs in *Table 4* are based on the ability of the CNSP to maintain chemical and physical stability and to suppress microbial growth. These BUDs represent the limit for CNSPs that are packaged in tight, light-resistant containers unless conditions in *10.4 CNSPs Requiring Shorter BUDs* or *10.5 Extending BUDs for CNSPs* apply.

The aqueous and nonaqueous dosage forms in *Table 4* are defined based on the water activity (a_w) of the most similar drug preparations described in *Table 3* or *Application of Water Activity Determination to Nonsterile Pharmaceutical Products* ⟨1112⟩. In general, the use of a_w aids in assessing the susceptibility of CNSPs to microbial contamination and the potential for API degradation due to hydrolysis. The a_w is different from the water content and may be considered as the available water to support microbial growth and hydrolytic reactions. Nonaqueous dosage forms will not support spore germination or microbial growth due to their low a_w. Reduced a_w greatly assists in the prevention of microbial proliferation in conventionally manufactured products and is expected to convey the same benefit to CNSPs.

Compounders are not required to measure a_w for CNSPs. While the manufactured products in ⟨1112⟩, *Table 2* and compounded preparations in *Table 3* below are not exhaustive, they provide examples of dosage forms that have an $a_w < 0.6$ and those that have an $a_w \geq 0.6$ and can assist personnel in determining the BUD by dosage form using *Table 4*.

When preparing CNSPs, raw materials and equipment contribute a bioburden to the final preparation. CNSPs with an $a_w \geq 0.6$, and a BUD within the limits of *Table 4*, should contain suitable antimicrobial agents to protect against the proliferation of bacteria, yeast, and mold contamination that may be inadvertently introduced anytime during the compounding process or throughout the BUD under appropriate handling and storage conditions. All CNSPs with an extended BUD must follow *10.5 Extending BUDs for CNSPs*. Careful consideration should be taken when selecting a preservative to ensure microbiological effectiveness and stability. When antimicrobial preservatives are contraindicated in a CNSP, storage of the preparation in a refrigerator is required if such storage does not change the physical or chemical properties of the CNSP (i.e., precipitation).

Table 3. Water Activity of Common Compounded Nonsterile Dosage Forms[a]

Nonaqueous Dosage Forms: $a_w < 0.6$			Aqueous Dosage Forms: $a_w \geq 0.6$		
Dosage Form	**Description**	a_w	**Dosage Form**	**Description**	a_w
Animal treat	Animal treat (oil flavor)	0.507	Animal treat	Animal treat with 15%–18% aqueous flavor	0.716
Capsule (oil filled)	Olive oil encapsulated	0.468	Cream	Cream vehicle (oil in water emulsion, petrolatum free)	0.968
Capsule (powder filled)	Powder base encapsulated	0.435	Cream	Emollient cream (petrolatum and mineral oil)	0.984
Gel (glycol based)	Propylene glycol, ethoxy diglycol, hydroxypropyl cellulose gel	0.056	Cream	Cream (oil in water emulsion with natural oils)	0.989
Lollipop (sorbitol based)	Sorbitol-based lollipop	0.460	Foam	Foaming surfactant solution	0.983
Ointment	Hydrophilic petrolatum	0.396	Gel (water based)	Alcohol-free aqueous gel	0.990
Ointment	Polyethylene and mineral oil gel base	0.459	Gel (water based)	Hydroxypropyl methylcellulose (HPMC) gel	1.000
Oral solution (glycol based)	20% Polyethylene glycol and 80% propylene glycol	0.009	Lotion	Lotion (oil in water emulsion)	0.986
Oral solution (oil based)	Medium chain triglycerides oil	0.338	Nasal spray	Nasal spray	0.991
Oral suspension (fixed oil)	Fixed oil with thickener	0.403	Oral solution (water based)	Low-sucrose syrup vehicle	0.906

Table 3. Water Activity of Common Compounded Nonsterile Dosage Forms[a] *(continued)*

Nonaqueous Dosage Forms: $a_w < 0.6$			Aqueous Dosage Forms: $a_w \geq 0.6$		
Dosage Form	**Description**	a_w	**Dosage Form**	**Description**	a_w
Powder for inhalation	Encapsulated powder for inhalation	0.402	Oral solution (water based)	90% Water and 10% glycerin	0.958
Stick	Lip balm	0.181	Oral suspension (water based)	Oral suspension base	0.992
Suppository	Polyethylene glycol base	0.374	Rinse	Polymer gel with 30% water	0.960
Suppository	Fatty acid base	0.385	Shampoo	Shampoo	0.976
Tablet (compressed)	Compressed tablet	0.465	Simple syrup	Simple syrup	0.831
Tablet (triturate)	Tablet triturate (lactose and/or sucrose)	0.427	—	—	—
Troche or lozenge (gelatin based)	Gelatin troche or lozenge with NMT 3% aqueous flavor	0.332	—	—	—
Troche or lozenge (glycol based)	Polyethylene glycol troche or lozenge with NMT 3% aqueous flavor	0.571	—	—	—

[a] The measured a_w values in *Table 3* for the different dosage forms are intended to be representative examples. The descriptions listed are details about the tested formulation and are provided to assist personnel in determining whether their CNSPs are aqueous or nonaqueous.

Table 4. BUD Limit by Type of Preparation in the Absence of a *USP–NF* Compounded Preparation Monograph or CNSP-Specific Stability Information[a]

Type of Preparation	BUD (days)	Storage Temperature[b]
Aqueous Dosage Forms ($a_w \geq 0.60$)		
Nonpreserved aqueous dosage forms[c]	14	Refrigerator
Preserved aqueous dosage forms[c]	35	Controlled room temperature or refrigerator
Nonaqueous Dosage Forms ($a_w < 0.60$)		
Oral liquids (nonaqueous)[d]	90	Controlled room temperature or refrigerator
Other nonaqueous dosage forms[e]	180	Controlled room temperature or refrigerator

[a] A shorter BUD must be assigned when the physical and chemical stability of the CNSP is less than the BUD limit stated in the table (see *10.4 CNSPs Requiring Shorter BUDs*).
[b] See *Packaging and Storage Requirements* ⟨659⟩.
[c] An aqueous preparation is one that has an $a_w \geq 0.6$ (e.g., emulsions, gels, creams, solutions, sprays, or suspensions).
[d] A nonaqueous oral liquid is one that has an $a_w < 0.6$.
[e] Other nonaqueous dosage forms that have an $a_w < 0.6$ (e.g., capsules, tablets, granules, powders, nonaqueous topicals, suppositories, and troches or lozenges).

10.4 CNSPs Requiring Shorter BUDs

The BUDs in *Table 4* are the BUD limits for CNSPs in the absence of specific stability information. This does not absolve the designated person(s) from performing due diligence to determine if there is existing stability data that would require a shorter BUD.

Additionally,

- The BUD of the CNSP must not exceed the shortest remaining expiration date of any of the commercially available starting components.
- For CNSPs prepared from one or more compounded components, the BUD should generally not exceed the shortest BUD of any of the individual compounded components. However, there may be acceptable instances when the BUD of the final CNSP exceeds the BUD assigned to compounded components (e.g., pH-altering solutions). If the assigned BUD of the final CNSP exceeds the BUD of the compounded components, the physical, chemical, and microbiological quality of the final CNSP must not be negatively impacted.

10.5 Extending BUDs for CNSPs

- *CNSPs with a USP–NF monograph:* When compounding from a *USP–NF* compounded preparation monograph for the CNSP, the BUD must not exceed the BUD specified in the monograph.
- *CNSPs with stability information:* If there is a stability study using a stability-indicating analytical method for the API(s), CNSP formulation, and material of composition of the container closure that will be used, then the BUD indicated by the study may be used in lieu of the BUDs specified in *Table 4* for aqueous and nonaqueous dosage forms, up to a maximum of 180 days.

If the BUD of the CNSP is extended beyond the BUDs in *Table 4*, an aqueous CNSP must be tested for antimicrobial effectiveness (see *Antimicrobial Effectiveness Testing* ⟨51⟩). The designated person(s) may rely on antimicrobial effectiveness testing that is conducted (or contracted for) once for each formulation in the particular container closure system—including materials of composition of the container closure system—in which it will be packaged. Alternatively,

the designated person(s) may rely on antimicrobial effectiveness testing results provided by an FDA-registered facility or published in peer-reviewed literature as long as the CNSP formulation (including any preservative) and container closure materials of composition are the same as those tested (unless a bracketing study is performed). When a bracketing study is performed, antimicrobial effectiveness testing may be performed on a low concentration and on a high concentration of the active ingredient in the formulation to establish preservative effectiveness across various strengths of the same formulation (e.g., bracketing). The concentration of all other ingredients (including preservatives) must fall within the bracketed range.

11. SOPS

Facilities preparing CNSPs must develop SOPs on all aspects of the compounding operation. All personnel who conduct or oversee compounding activities must be trained in the facility's SOPs and be responsible for ensuring that they are followed.

One or more person(s) must be designated to ensure that the facility's SOPs are fully implemented. The designated person(s) must ensure that follow-up occurs if problems, deviations, or errors are identified.

12. QUALITY ASSURANCE AND QUALITY CONTROL

Quality assurance (QA) is a system of procedures, activities, and oversight that ensures that the compounding process consistently meets quality standards. Quality control (QC) is the sampling, testing, and documentation of results that, taken together, ensure that specifications have been met before release of the CNSP. See *Quality Assurance in Pharmaceutical Compounding* ⟨1163⟩.

A facility's QA and QC programs must be formally established and documented in the facility's SOPs that ensure that all aspects of the preparation of CNSPs are conducted in accordance with the requirements in this chapter (⟨795⟩) and the laws and regulations of the applicable regulatory jurisdiction. Designated person(s) must ensure that the facility has formal, written QA and QC programs that establish a system of

1. Adherence to procedures,
2. Prevention and detection of errors and other quality problems,
3. Evaluation of complaints and adverse events, and
4. Appropriate investigations and corrective actions.

The facility's SOPs must describe the roles, duties, and training of the personnel responsible for each aspect of the QA program. Designated person(s) responsible for the QA program must have the training, experience, responsibility, and authority to perform these duties. The overall QA and QC program must be reviewed at least once every 12 months by the designated person(s). The results of the review must be documented, and appropriate action must be taken if needed.

12.1 Notification About and Recall of Dispensed CNSPs

The facility must have procedures in place to

- Determine when recalls must be initiated, which should include procedures to immediately notify the prescriber of a failure of specifications with the potential to cause patient harm (e.g., strength, purity, or other quality attributes)
- Recall any unused dispensed CNSPs and quarantine any stock remaining in the pharmacy
- Investigate if other lots are affected and recall if necessary

An SOP for recall of dispensed CNSPs must contain

- Procedures to determine the severity of the problem and the urgency for implementation and completion of the recall
- Procedures to determine the distribution of any affected CNSP, including the data and quantity of distribution
- Procedures to identify patients who have received the CNSP
- Procedures for disposal and documentation of the recalled CNSP
- Procedures to investigate and document the reason for recall

The nonsterile compounding facility must document the implementation of the recall procedures. The recall must be reported to appropriate regulatory bodies as required by the laws and regulations of the applicable regulatory jurisdiction.

12.2 Complaint Handling

Compounding facilities must develop and implement SOPs for handling complaints. Complaints may include but are not limited to concerns or reports on the quality, labeling, or possible adverse reactions related to a specific CNSP.

A designated person(s) must review all complaints to determine whether the complaint indicates a potential quality problem with the CNSP. If it does, a thorough investigation into the cause of the problem must be initiated and completed. The investigation must consider whether the quality problem extends to other CNSPs. Corrective action, if necessary, must be implemented for all potentially affected CNSPs.

Consider whether to initiate a recall of potentially affected CNSPs and whether to cease nonsterile compounding processes until all underlying problems have been identified and corrected.

A readily retrievable written or electronic record of each complaint must be kept by the facility, regardless of the source of the complaint (e.g., email, telephone, or mail). The record must contain the name of the complainant or other unique identifier, the date the complaint was received, the nature of the complaint, and the response to the complaint. In addition, to the extent that the information is known, the following should be recorded: the name and strength of the CNSP and the assigned internal identification number (e.g., prescription, order, or lot number).

The record must also include the findings of any investigation and any follow-up. Records of complaints must be easily retrievable for review and evaluation for possible trends and must be retained in accordance with the record-keeping requirements in *14. Documentation*. A CNSP that is returned in connection with a complaint must be quarantined until it is destroyed after completion of the investigation and in accordance with laws and regulations of the applicable regulatory jurisdiction.

12.3 Adverse Event Reporting

Adverse events potentially associated with the quality of CNSPs must be reported in accordance with the facility's SOPs and all laws and regulations of the applicable regulatory jurisdiction. If the investigation into an adverse event reveals a quality problem with a CNSP that is likely to affect other patients, those patients and prescribers potentially affected must be informed.

13. CNSP PACKAGING AND TRANSPORTING

13.1 Packaging of CNSPs

The facility's SOPs must describe packaging of CNSPs. Personnel should select and use packaging materials that will maintain the physical and chemical integrity and stability of the CNSPs. Packaging materials must protect CNSPs from damage, leakage, contamination, and degradation, while simultaneously protecting personnel from exposure.

13.2 Transporting of CNSPs

If transporting CNSPs, the facility must have written SOPs to describe the mode of transportation, any special handling instructions, and whether temperature monitoring devices are needed.

14. DOCUMENTATION

All facilities where CNSPs are prepared must have and maintain written or electronic documentation to demonstrate compliance with the requirements in this chapter. This documentation must include, but is not limited to, the following:

- Personnel training, competency assessments, and qualification records including corrective actions for any failures
- Equipment records (e.g., calibration, verification, and maintenance reports)
- COAs and all documentation required for components not conventionally manufactured
- Receipt of components
- SOPs, MFRs, and CRs
- Release inspection and testing records
- Information related to complaints and adverse events including corrective actions taken
- Results of investigations and corrective actions
- Records of cleaning and sanitizing the designated compounding area
- Temperature logs
- Accommodations to personnel compounding CNSPs
- Any required routine review (e.g., yearly review of QA and QC programs, yearly review of chemical hazard and disposal information)

Documentation must comply with all laws and regulations of the applicable regulatory jurisdiction. Records must be legible and stored in a manner that prevents their deterioration and/or loss. All required CRs for a particular CNSP (e.g., MFR, CR, and release inspection and testing results) must be readily retrievable for at least 2 years after preparation or as required by the laws and regulations of the applicable regulatory jurisdiction, whichever is longer.

GLOSSARY

Active pharmaceutical ingredient (API): Any substance or mixture of substances intended to be used in the compounding of a preparation, thereby becoming the active ingredient in that preparation and furnishing pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease in humans or animals or affecting the structure and function of the body. Also referred to as *Bulk drug substance*. A conventionally manufactured drug product is not an API but is typically manufactured from an API(s).

Added substance: An ingredient that is necessary to compound a preparation but is not intended or expected to cause a pharmacologic response if administered alone in the amount or concentration contained in a single dose of the compounded preparation. The term is used synonymously with inactive ingredient, excipient, and pharmaceutical ingredient.

Administration: The preparation of a nonsterile pharmacologic or other therapeutic agent for ingesting, inserting, applying, or otherwise providing a nonsterile medication in its final form to a single patient. This includes crushing a tablet(s) or opening a capsule(s) to mix with food or liquids to facilitate patient dosing.

Alcohol-based hand rub: An alcohol-containing preparation (liquid, gel, or foam) designed for application to the hands of healthcare personnel to inactivate microorganisms and/or temporarily suppress their growth. Such preparations may contain one or more types of alcohol, other active ingredients, excipients, and humectants.

Assigned trainer: One or more individuals assigned by the designated person(s) to be responsible and accountable for directly providing the training, observation, and/or evaluation of personnel for the preparation of CNSPs.

Beyond-use date (BUD): The date, or hour and date, after which a CNSP must not be used, stored, or transported. The date is determined from the date or time the preparation is compounded.

Biological safety cabinet (BSC): A ventilated cabinet that may be used for compounding. These cabinets are divided into three general classes (Class I, Class II, and Class III). Class II BSCs are further divided into types (Type A1, Type A2, Type B1, Type B2, and Type C1).

Bulk drug substance: See the entry for *Active pharmaceutical ingredient*.

Certificate of analysis (COA): A report from the supplier of a component, container, or closure that accompanies the supplier's material and contains the specifications and results of all analyses and a description of the material.

Cleaning: The process of removing substances (e.g., organic and inorganic material) from objects and surfaces, normally accomplished by manually or mechanically using water with detergents or enzymatic products.

Cleaning agent: An agent, usually containing a surfactant, used for the removal of substances (e.g., dirt, debris, microbes, and residual drugs or chemicals) from surfaces.

Closed-system processing device: A device designed to reduce the potential exposure to personnel or contamination of the facility or CNSPs. Examples include CVEs, BSCs, or single-use containment glove bags.

Component: Any ingredient used in the compounding of a preparation, including any API, added substance, or conventionally manufactured product.

Compounded nonsterile preparation (CNSP): A preparation not intended to be sterile that is created by combining, admixing, diluting, pooling, reconstituting other than as provided in the manufacturer's labeling, or otherwise altering a drug product or bulk drug substance.

Compounding: The process of combining, admixing, diluting, pooling, reconstituting other than as provided in the manufacturer's labeling, or otherwise altering a drug product or bulk drug substance to create a nonsterile preparation.

Compounding area: An area that is specifically designated for nonsterile compounding.

Compounding personnel: Personnel trained to compound or oversee compounding of preparations.

Compounding record (CR): Documents the compounding of each CNSP.

Container closure system: Packaging system components that together contain and protect the dosage form. This includes primary packaging system components and secondary packaging system components if the latter are intended to provide additional protection.

Containment glove bag: A single-use disposable glove bag that is capable of containing airborne chemical particles.

Containment ventilated enclosure (CVE): A full or partial enclosure that uses ventilation principles to capture, contain, and remove airborne contaminants through high-efficiency particulate air (HEPA) filtration and to prevent their release into the work environment.

Conventionally manufactured product: A pharmaceutical dosage form, usually the subject of an application approved by the applicable national regulatory agency, that is manufactured under current good manufacturing practice conditions.

Designated person(s): One or more individuals assigned to be responsible and accountable for the performance and operation of the facility and personnel as related to the preparation of CNSPs.

FDA: US Food and Drug Administration.

Formulation: The specific qualitative and quantitative composition of the final CNSP.

Hazardous drug (HD): Any drug identified by at least one of the following criteria: carcinogenicity, teratogenicity or developmental toxicity; reproductive toxicity in humans; organ toxicity at low dose in humans or animals; genotoxicity or new drugs that mimic existing HDs in structure or toxicity. See ⟨800⟩.

Label: The part of the labeling on the immediate container.

Labeling: All labels and other written, printed, or graphic matter on the immediate container or on or inside any packaging system or wrapper in which the article is enclosed, except for any outer shipping container.

Master formulation record (MFR): A detailed record of procedures that describes how the CNSP is to be prepared.

Monograph: A quality documentary standard within *USP–NF* that articulates the quality expectations for a medicine including for its identity, strength, purity, and performance. It also describes the tests to validate that a medicine and its ingredients meet these criteria.

Oversight: The review, monitoring, and supervision of actions taken by personnel; bearing responsibility for those actions; and being available if and when needed for consultation even if not physically present.

Preservative: A substance added to inhibit microbial growth.

Purified water: The minimal quality of source water for the production of *Purified Water* is drinking water whose attributes are prescribed by the US Environmental Protection Agency (EPA), the European Union, Japan, or the World Health Organization (WHO). This source water may be purified using unit operations that include deionization, distillation, ion exchange, reverse osmosis, filtration, or other suitable purification procedures. (See ⟨1231⟩*, 3.1.1 Purified Water*.)

Quality assurance (QA): A system of procedures, activities, and oversight that ensures that the compounding process consistently meets quality standards.

Quality control (QC): The sampling, testing, and documentation of results that, taken together, ensure that specifications have been met for the CNSP.

Reconstitution: The process of adding a diluent to a conventionally manufactured product to prepare a solution or suspension.

Release inspection and testing: Visual inspection and testing performed to ensure that a preparation meets appropriate quality characteristics.

Sanitizing agent: An agent for reducing, on inanimate surfaces, the number of microorganisms (e.g., 70% isopropyl alcohol).

SDS: Safety data sheet.

SOP: Standard operating procedure.

Specification: The tests, analytical methods, and acceptance criteria to which any components, CNSP, container closure system, equipment, or other material used in the compounding of CNSPs must conform to be considered acceptable for its intended use.

Stability: The extent to which a product or preparation retains physical and chemical properties and characteristics within specified limits throughout its expiration or BUD.

Verify: To confirm that a method, process, system, or equipment will perform as expected under the conditions of actual use.

Water activity (a_w): A measure of the fraction of total water that is unbound and freely available to participate in chemical, biochemical, or physicochemical reactions or provide an environment that can support microbial growth. Note that a_w is not water content.▲ (Official 1-Nov-2023)

⟨797⟩ PHARMACEUTICAL COMPOUNDING—STERILE PREPARATIONS

Change to read:

▲1. INTRODUCTION AND SCOPE

This chapter describes the minimum standards to be followed for the preparation of compounded sterile preparations (CSPs) for human and animal drugs. Sterile compounding is defined as combining, admixing, diluting, pooling, reconstituting, repackaging, or otherwise altering a drug product or bulk drug substance to create a sterile preparation.

The requirements in this chapter must be followed to minimize harm, including death, to human and animal patients that could result from 1) microbial contamination [nonsterility], 2) excessive bacterial endotoxins, 3) variability from the intended strength of correct ingredients, 4) physical and chemical incompatibilities, 5) chemical and physical contaminants, and/or 6) use of ingredients of inappropriate quality.

Aseptic techniques, processes, and procedures must be followed for preparing any sterile medication. Processes and procedures must be in place to minimize the potential for contact with nonsterile surfaces, introduction of particulate matter or biological fluids, and mix-ups with other products or CSPs.

The use of technologies, techniques, materials, and procedures other than those described in this chapter is not prohibited as long as they are noninferior to those described herein and validated for the intended purpose (e.g., *Validation of Alternative Microbiological Methods* ⟨1223⟩ and *Validation of Compendial Procedures* ⟨1225⟩).

Unless otherwise specified in each section, the requirements of this chapter apply to compounding all categories of CSPs.

1.1 Scope

1.1.1 CSPs affected: The requirements in this chapter must be met to ensure the sterility of any CSP. Although the list below is not exhaustive, the following must be sterile:

- Injections, including infusions
- Irrigations for internal body cavities (i.e., any space that does not normally communicate with the environment outside of the body, such as the bladder cavity or peritoneal cavity). [NOTE—Irrigations for the mouth, rectal cavity, and sinus cavity are not required to be sterile.]
- Ophthalmic dosage forms
- Aqueous preparations for pulmonary inhalation. [NOTE—Nasal dosage forms intended for local application are not required to be sterile.]
- Baths and soaks for live organs and tissues
- Implants

1.1.2 Specific practices

Allergenic extracts: Licensed allergenic extracts are mixed and diluted to prepare prescription sets for administration to patients. A prescription set is a vial or set of vials of premixed licensed allergenic extracts for subcutaneous immunotherapy that have been diluted with an appropriate diluent for an individual patient. Because of certain characteristics of allergenic extracts and allergy practice, preparation of allergenic extract prescription sets is not subject to all of the requirements in this chapter that are applicable to other sterile CSPs. The standards for compounding allergenic extracts, which are described in *21. Compounding Allergenic Extracts*, are applicable only when

1. The compounding process involves transfer via sterile needles and syringes of conventionally manufactured sterile allergen products and appropriate conventionally manufactured sterile added substances; and
2. Manipulations are limited to penetrating stoppers on vials with sterile needles and syringes and transferring sterile liquids in sterile syringes to sterile vials.

Blood-derived and other biological materials: When compounding activities require the manipulation of a patient's blood-derived or other biological material (e.g., autologous serum), the manipulations must be clearly separated from other compounding activities and equipment used in CSP preparation activities, and they must be controlled by specific standard operating procedures (SOPs) to avoid any cross-contamination. Handling of blood components and other biological materials must additionally comply with laws and regulations of the applicable regulatory jurisdiction.

Hazardous drugs: Handling of sterile hazardous drugs (HDs) must additionally comply with *Hazardous Drugs—Handling in Healthcare Settings* ⟨800⟩.

Repackaging: Repackaging of a sterile product or preparation from its original container into another container must be performed in accordance with the requirements in this chapter.

Sterile radiopharmaceuticals: Compounding of radiopharmaceuticals is not required to meet the standards of this chapter as they are subject to the requirements in *Radiopharmaceuticals—Preparation, Compounding, Dispensing, and Repackaging* ⟨825⟩.

1.1.3 Personnel and settings affected: This chapter describes the minimum requirements that apply to all persons who prepare CSPs and all places where CSPs are prepared. This includes but is not limited to pharmacists, technicians, nurses, physicians, veterinarians, dentists, naturopaths, and chiropractors in all places including but not limited to hospitals and other healthcare institutions, medical and surgical patient treatment sites, infusion facilities, pharmacies, and physician or veterinarian practice sites. Any person entering a sterile compounding area, whether preparing a CSP or not, must meet the requirements in *3. Personal Hygiene and Garbing*.

The compounding facility must designate one or more individuals (i.e., the designated person(s)) to be responsible and accountable for the performance and operation of the facility and personnel in the preparation of CSPs and for performing other functions as described in this chapter.

1.2 Administration

For the purposes of this chapter, "administration" means the direct application of a sterile product or preparation to a single patient by injecting, infusing, or otherwise providing a sterile product or preparation in its final form.

Administration of medication is out of the scope of this chapter. Standard precautions such as the Centers for Disease Control and Prevention (CDC) safe injection practices apply to administration. See ⟨800⟩ for additional recommendations for the administration of hazardous drugs.

1.3 Immediate-Use CSPs

When all of the following conditions are met, compounding of CSPs for direct and immediate administration is not subject to the requirements for Category 1, Category 2, or Category 3 CSPs:

1. Aseptic techniques, processes, and procedures are followed, and written SOPs are in place to minimize the potential for contact with nonsterile surfaces, introduction of particulate matter or biological fluids, and mix-ups with other conventionally manufactured products or CSPs.
2. Personnel are trained and demonstrate competency in aseptic processes as they relate to assigned tasks and the facility's SOPs.
3. The preparation is performed in accordance with evidence-based information for physical and chemical compatibility of the drugs (e.g., approved labeling, stability and compatibility studies).
4. The preparation involves not more than 3 different sterile products.
5. Any unused starting component from a single-dose container must be discarded after preparation is complete. Single-dose containers must not be used for more than one patient.
6. Administration begins within 4 h following the start of preparation. If administration has not begun within 4 h following the start of preparation, it must be promptly, appropriately, and safely discarded.
7. Unless directly administered by the person who prepared it or administration is witnessed by the preparer, the CSP must be labeled with the names and amounts of all active ingredients, the name or initials of the person who prepared the preparation, and the 4-h time period within which administration must begin.

Handling of sterile hazardous drugs (HDs) must additionally comply with ⟨800⟩.

1.4 Preparation Per Approved Labeling

Compounding does not include mixing, reconstituting, or other such acts that are performed in accordance with directions contained in approved labeling or supplemental materials provided by the product's manufacturer.

Preparing a conventionally manufactured sterile product in accordance with the directions in the manufacturer's approved labeling is out of scope of this chapter only if

1. The product is prepared as a single dose for an individual patient; and
2. The approved labeling includes information for the diluent, the resultant strength, the container closure system, and storage time.

See ⟨800⟩ for additional recommendations for the preparation of hazardous drugs.

Proprietary bag and vial systems: Docking and activation of proprietary bag and vial systems in accordance with the manufacturer's labeling for *immediate* administration to an individual patient is not considered compounding and may be performed outside of an International Organization for Standardization (ISO) Class 5 environment.

Docking of the proprietary bag and vial systems for *future activation* and administration is considered compounding and must be performed in an ISO Class 5 environment in accordance with this chapter, with the exception of *14. Establishing Beyond-Use Dates*. Beyond-use dates (BUDs) for proprietary bag and vial systems must not be longer than those specified in the manufacturer's labeling.

1.5 CSP Categories

This chapter distinguishes three categories of CSPs: Category 1, Category 2, and Category 3, primarily based on the state of environmental control under which they are compounded, the probability for microbial growth during the time they will be stored, and the time period within which they must be used.

Category 1 CSPs are compounded under the least controlled environmental conditions and therefore are assigned a BUD of 12 h or less at controlled room temperature or 24 h or less when refrigerated, if compounded in accordance with all of the applicable requirements for Category 1 CSPs in this chapter.

Category 2 CSPs require more environmental controls and testing than Category 1 CSPs and may be assigned a BUD of greater than 12 h at controlled room temperature or more than 24 h if refrigerated, but not exceed the limits established in *Table 13* (see *14. Establishing Beyond-Use Dates*), if compounded in accordance with all of the applicable requirements for Category 2 CSPs in this chapter.

Category 3 CSPs undergo sterility testing, supplemented by endotoxin testing when applicable, and have more requirements than Category 2 CSPs for personnel qualification, use of sterile garb, use of sporicidal disinfectants, frequency of environmental monitoring, and stability determination. Category 3 CSPs may be assigned longer BUDs than those set for Category 2 CSPs but not exceeding the limits in *Table 14* (see *14. Establishing Beyond-Use Dates*), if compounded in accordance with all applicable requirements for Category 3 CSPs in this chapter (see *14.4 Additional Requirements for Category 3 CSPs*).

The requirements that are not specifically described as applicable to Category 1, Category 2, or Category 3, are applicable to the compounding of all CSPs unless the CSP is otherwise described in *1.1 Scope*.

Category 1, Category 2, and Category 3 CSPs can be compounded by using only sterile starting ingredients, or by using some or all nonsterile starting ingredients. If all components used to compound are sterile from the start, the sterility of the components must be maintained during compounding to produce a CSP.

If one or more of the starting components being used to compound is not sterile, the sterility of the compounded preparation must be achieved through a sterilization process (e.g., terminal sterilization in the final sealed container) or sterilizing filtration, and then sterility must be maintained if the CSP is subsequently manipulated. When compounding with nonsterile starting components, supplies, or equipment, the quality of the components, the

effectiveness of the sterilization step, and bacterial endotoxin mitigation strategies are critical to achieving a sterile preparation that is free from excessive bacterial endotoxins.

2. PERSONNEL TRAINING AND EVALUATION

All personnel who compound or have direct oversight of compounding personnel must be initially trained and qualified by demonstrating knowledge and competency in compounding CSPs according to the requirements in this section before being allowed to perform their job functions independently. Designated person(s) are responsible for creating and implementing a training program for personnel and for ensuring that compounders, personnel who have direct oversight of compounders, and personnel who perform restocking or cleaning and disinfection duties are initially trained and qualified by demonstrating knowledge and competency in maintaining the quality of the sterile compounding environment before being allowed to perform their job functions independently. Training and observation may be performed by the designated person(s) or an assigned trainer. Personnel who compound or have direct oversight of compounding personnel must complete training initially and at least every 12 months in appropriate sterile compounding principles and practices as described below (see *2.1 Demonstrating Knowledge and Competency of Core Skills*). Personnel who only perform restocking or cleaning and disinfecting duties outside of the primary engineering control (PEC) must complete ongoing training as required by the facility's SOPs. Personnel compounding only immediate-use CSPs must complete training as required by the facility's SOPs (see *1.3 Immediate-Use CSPs*).

Each compounding facility must develop a written training program that describes the required training, the frequency of training, and the process for evaluating the performance of individuals who compound, have direct oversight of compounding personnel, perform in-process checks, final verification, and dispensing of CSPs. This program must equip personnel with the appropriate knowledge and train them in the required skills necessary to perform their assigned tasks, and SOPs should specify the training required for such tasks.

Training and evaluation of personnel must be documented (see *20. Documentation*).

2.1 Demonstrating Knowledge and Competency of Core Skills

Before beginning to compound CSPs independently or have direct oversight of compounding personnel, personnel must complete training and be able to demonstrate knowledge of principles and competency of skills for performing sterile manipulations and achieving and maintaining appropriate environmental conditions as applicable to their assigned job functions. This must be completed initially and at least every 12 months in at least the following:

- Hand hygiene
- Garbing
- Cleaning and disinfection
- Calculations, measuring, and mixing
- Aseptic technique
- Achieving and/or maintaining sterility (and apyrogenicity if compounding with nonsterile components)
- Use of equipment
- Documentation of the compounding process (e.g., master formulation and compounding records)
- Principles of high-efficiency particulate air (HEPA)-filtered unidirectional airflow within the ISO Class 5 area
- Proper use of PECs
- Principles of movement of materials and personnel within the compounding area

If the facility has only one person in the compounding operation, that person must document that they have obtained training and demonstrated competency, and they must comply with the other requirements of this chapter.

2.2 Demonstrating Competency in Garbing and Hand Hygiene

Before beginning to compound Category 1, Category 2, or Category 3 CSPs or have direct oversight of compounding personnel, personnel must successfully complete an initial garbing competency evaluation no fewer than 3 separate times. The 3 successful completions must be in succession—failure of any of the 3 initial garbing competency evaluations requires repeat testing until personnel successfully complete 3 evaluations in a row. The garbing competency evaluation consists of a visual observation and gloved fingertip and thumb sampling (GFT) of both hands (see *Box 1*). Each of the 3 initial competency evaluations must occur after performing a separate and complete hand hygiene and full garbing procedure. All garbing competencies must be completed with gloved fingertip and thumb sampling after garbing (see *Box 1*) and a documented visual audit while performing hand hygiene and garbing procedures (see *3. Personal Hygiene and Garbing*). Gloved fingertip and thumb sampling after garbing, but before applying sterile 70% IPA to gloves, must be performed on donned sterile gloves on both hands in a classified area or segregated compounding area (SCA).

Failure is indicated by visual observation of improper hand hygiene and garbing procedures and/or gloved fingertip and thumb sampling results that exceed the action levels in *Table 1*. Results of the evaluation and corrective actions, in the event of failure, must be documented and the documentation maintained to provide a record and long-term assessment of personnel competency. Documentation must at a minimum include the name of the person evaluated; evaluation date and time; media and components used including manufacturer, expiration date, and lot number; starting temperature for each interval of incubation; dates of incubation; results and identification of the observer and personnel reading and documenting the results. Microbial identification of the colony-forming units (cfu) is not required for gloved fingertip and thumb sampling.

After the initial garbing competency evaluations, compounding personnel must successfully complete the garbing competency (see *Table 1*) at least one time every 6 months for personnel compounding Category 1 and Category 2 CSPs, and at least one time every 3 months for personnel compounding Category 3 CSPs. Personnel who have direct oversight of compounding personnel, but do not compound, must complete a garbing competency evaluation every 12 months. The evaluation should correspond to the type of garbing activities of the personnel they oversee. Personnel who have direct oversight of compounding personnel must not compound unless they successfully complete the garbing competency evaluation at the same intervals required for compounding personnel.

Box 1. Gloved Fingertip and Thumb Sampling Procedures

- Use one sampling media device (e.g., plates, paddles, or slides) per hand, containing general microbial growth agar (e.g., trypticase soy agar [TSA]) supplemented with neutralizing additives (e.g., lecithin and polysorbate 80) as this agar supports both bacterial and fungal growth.
- Label each media device with a personnel identifier, right or left hand, and the date and time of sampling.
- Do not apply sterile 70% isopropyl alcohol (IPA) to gloves immediately before touching the media device because this could cause a false-negative result. Using a separate media device for each hand, collect samples from all gloved fingertips and thumbs from both hands by rolling fingertip pads and thumb pad over the agar surface.
- Incubate the media device at 30°–35° for no less than 48 h and then at 20°–25° for no less than 5 additional days. Samples must be incubated in an incubator. Handle and store media devices to avoid contamination and prevent condensate from dropping onto the agar during incubation and affecting the accuracy of the cfu reading (e.g., invert plates).
- Record the number of cfu per hand (left hand, right hand).
- Determine whether the cfu action level is exceeded by counting the total number of cfu from both hands.

2.3 Competency Testing in Aseptic Manipulation

Before beginning to compound Category 1, Category 2, or Category 3 CSPs independently or have direct oversight of compounding personnel, personnel must successfully complete an aseptic manipulation competency evaluation. The aseptic manipulation competency evaluation consists of a visual observation, media-fill testing, followed by a gloved fingertip and thumb sampling on both hands, and surface sampling of the direct compounding area to assess aseptic technique and related practices (see *Box 2*).

For personnel compounding Category 1 and Category 2 CSPs, the aseptic manipulation competency must occur initially and at least every 6 months thereafter. For personnel compounding Category 3 CSPs, the aseptic manipulation competency must occur initially and at least every 3 months thereafter. Personnel who have direct oversight of compounding personnel must complete an aseptic manipulation competency evaluation annually. The evaluation should correspond to the type of activities of the personnel they oversee but does not require the same quantities. Personnel who have direct oversight of compounding personnel must not compound unless they successfully complete the aseptic manipulation competency evaluation that simulates the most difficult and challenging aseptic compounding procedures encountered by the person at the same intervals required for compounding personnel.

When performing a media-fill test, simulate the most difficult and challenging aseptic compounding procedures encountered by the person replacing all the components used in the CSPs with soybean–casein digest media. The simulation must capture elements that could potentially affect the sterility of the CSP including but not limited to:

- Factors associated with the length of the process that can pose contamination risk (e.g., operator fatigue, quality of equipment)
- Number of aseptic additions or transfers
- Number, type, and complexity of manipulations
- Number of personnel in the buffer room or SCA

If using commercial sterile microbial growth media, a certificate of analysis (COA) must be obtained from the supplier stating that the lot of the growth media will support the growth of microorganisms. Store microbial growth media in accordance with manufacturer instructions and initiate the media-fill test by the expiration date of the media. If preparing sterile microbial growth media in-house for sterile-to-sterile media-fill testing, the growth promotion capability of the media must be demonstrated for each batch and documented as described in *Sterility Tests* ⟨71⟩, *Culture Media and Incubation Temperatures, Growth Promotion Test of Aerobes, Anaerobes, and Fungi*.

Failure is indicated by visible turbidity or other visual manifestations of growth in the media in one or more container closure unit(s) on or before the end of the incubation period. Microbial identification of the cfu is not required for media-fill testing.

Immediately following the media-fill test, gloved fingertip and thumb sampling must be performed on both hands and inside of an ISO Class 5 PEC. If conducting gloved fingertip and thumb sampling in a compounding aseptic isolator (CAI), compounding aseptic containment isolator (CACI), or a pharmaceutical isolator, samples must be taken from the sterile gloves placed over the gloves attached to the restricted-access barrier system (RABS) or pharmaceutical isolator sleeves.

Successful completion of the gloved fingertip and thumb sampling after media-fill testing is defined as ≤3 cfu as a total from both hands. See *Table 1* for action levels for gloved fingertip and thumb sampling results. Microbial identification of the cfu is not required for gloved fingertip and thumb sampling.

Surface sampling of the direct compounding area must occur in accordance with the requirements in *6.3 Monitoring Surfaces for Viable Particles*. A failure in the media fill, gloved fingertip and thumb sampling, or surface sample constitutes an overall failure of the aseptic manipulation competency.

Results of the evaluation and corrective actions must be documented and the documentation maintained to provide a record and long-term assessment of personnel competency. Documentation must at a minimum include 1) the name of the person evaluated, 2) evaluation date and time, 3) media and components used including their manufacturer or supplier, 4) expiration dates and lot numbers, 5) starting temperature for each interval of incubation, 6) dates of incubation, 7) the results, and 8) the names or other identification of the observer and the person who reads and documents the results.

Box 2. Media-Fill Testing Procedures

- If all of the starting components are sterile to begin with, manipulate them in a manner that simulates sterile-to-sterile compounding activities, and transfer the sterile soybean–casein digest media into the same types of container closure systems commonly used at the facility. Do not further dilute the media unless specified by the manufacturer.
- If some of the starting components are nonsterile to begin with, dissolve a commercially available nonsterile soybean–casein digest powder in nonbacteriostatic water to make a 3% nonsterile solution. Manipulate it in a manner that simulates nonsterile-to-sterile compounding activities. Prepare at least 1 container as the positive control to demonstrate growth promotion, which is indicated by visible turbidity upon incubation.
- Once the compounding simulation is completed and the final containers are filled with the test media, perform a gloved fingertip and thumb sample on each hand and surface sample of the direct compounding area inside the PEC. Take the samples prior to disinfecting gloves and PEC. Handle and store samples to avoid contamination and prevent condensate from dropping onto the agar during incubation and affecting the accuracy of the cfu reading (e.g., invert containers).
- Incubate the final containers at 20°–25° and 30°–35° for a minimum of 7 days at each temperature band to detect a broad spectrum of microorganisms. The order of the incubation temperatures must be described in the facility's SOPs. Final containers must be incubated in an incubator.
- Failure is indicated by visible turbidity or other visual manifestations of growth in the media in one or more container closure unit(s) on or before 14 days.

Table 1. Action Levels for Gloved Fingertip and Thumb Sampling[a]

Gloved Fingertip and Thumb Sampling	Action Levels (cfu, total from both hands)
After garbing	>0
After media-fill testing	>3

[a] Action levels are based on the total cfu count from both hands.

Table 2. Initial Training and Competency

Personnel Function	Defined by Facility SOPs	Required in ⟨797⟩ and Supplemented by Facility SOPs			
		Training and Competency in Maintaining the Quality of the Sterile Compounding Environment	Training and Competency in Sterile Compounding Principles and Practices	Garbing Competency (Including GFT)	Media Fill with Post-GFT and Surface Sampling
Compounder		X	X	X	X
Designated person and personnel with direct oversight of compounding personnel		X	X	X	X
Personnel who restock or clean and disinfect the sterile compounding area[a]	X				
Personnel who perform in-process checks or final verification of CSPs[a]	X				
Personnel who only compound immediate-use CSPs	X				
Others (e.g., maintenance personnel, certifiers, contractors, inspectors, surveyors)[a]	X				

[a] Personnel who do not compound nor have direct oversight of compounding personnel.

Table 3. Ongoing Training and Competency

Personnel Function	Defined by Facility SOPs	Required ⟨797⟩ and Supplemented by Facility SOPs		
		Training and Competency in Sterile Compounding Principles and Practices	Garbing Competency (Including GFT)	Media Fill with Post-GFT and Surface Sampling
Compounder		At least every 12 months	Category 1 and 2 at least every 6 months Category 3 at least every 3 months	Category 1 and 2 at least every 6 months Category 3 at least every 3 months
Designated person and personnel with direct oversight of compounding personnel		At least every 12 months unless compounding[a]	At least every 12 months unless compounding[a]	At least every 12 months unless compounding[a]
Personnel who restock or clean and disinfect the sterile compounding area[b]	X			

Table 3. Ongoing Training and Competency *(continued)*

Personnel Function	Defined by Facility SOPs	Required ⟨797⟩ and Supplemented by Facility SOPs		
		Training and Competency in Sterile Compounding Principles and Practices	Garbing Competency (Including GFT)	Media Fill with Post-GFT and Surface Sampling
Personnel who perform in-process checks or final verification of CSPs[b]	X			
Personnel who only compound immediate-use CSPs	X			
Others (e.g., maintenance personnel, certifiers, contractors, inspectors, surveyors)[b]	X			

[a] If compounding, follow compounder requirements.
[b] Personnel who do not compound or have direct oversight of compounding personnel.

3. PERSONAL HYGIENE AND GARBING

Personal hygiene and garbing are essential to maintain microbial control of the environment. Most microorganisms detected in cleanrooms are transferred from individuals. Squamous cells are normally shed from the human body at a rate of 10^6 or more per hour, and those skin particles are covered with microorganisms. Individuals entering a compounding area must be properly garbed and must maintain proper personal hygiene to minimize the risk of contamination to the environment and/or CSPs.

Individuals that may have a higher risk of contaminating the CSP and the environment (e.g., personnel with rashes, recent tattoos, oozing sores, conjunctivitis, or active respiratory infections) must report these conditions to the designated person(s). The designated person(s) is responsible for evaluating whether these individuals should be excluded from working in compounding areas before their conditions have resolved because of the risk of contaminating the CSPs and the environment.

3.1 Personnel Preparation

All personnel entering a compounding area where Category 1, Category 2, or Category 3 CSPs are prepared must take appropriate steps to minimize microbial contamination of the environment and of the CSPs, including hand hygiene (see *3.2 Hand Hygiene*), garbing (see *3.3 Garbing Requirements*), and consideration of needed materials to be brought into the compounding area.

Food (including mints, gum, etc.) and drinks must not enter anterooms, buffer rooms, or segregated compounding areas.

Before entering a compounding area, individuals must remove any items that are not easily cleanable or are not necessary for compounding. At a minimum, individuals must:

- Remove personal outer garments (e.g., bandanas, coats, hats, jackets, sweaters, vests)
- Remove all cosmetics because they shed flakes and particles
- Remove all hand, wrist, and other exposed jewelry, including piercings that could interfere with the effectiveness of garbing (e.g., the fit of gloves, cuffs of sleeves, and eye protection) or otherwise increase the risk of contamination of the CSP. Cover any jewelry that cannot be removed.
- Not wear earbuds or headphones
- Not bring electronic devices that are not necessary for compounding or other required tasks into the compounding area
- Keep nails clean and neatly trimmed to minimize particle shedding and avoid glove punctures. Nail products (e.g., polish, artificial nails, and extenders) must not be worn
- Wipe eyeglasses, if worn

The designated person(s) may permit accommodations to personnel preparation as long as the quality of the CSP and environment will not be affected. Accommodations must be documented.

3.2 Hand Hygiene

Any person entering a compounding area where Category 1, Category 2, or Category 3 CSPs are prepared must wash hands and forearms up to the elbows with soap and water before initiating compounding activities. Brushes must not be used for hand hygiene. Hand dryers must not be used. To minimize the risk of extrinsic contamination, disposable soap containers must not be refilled or topped off.

Box 3. Hand Washing Procedures

- Clean underneath fingernails under warm running water using a disposable nail cleaner.
- Wash hands and forearms up to the elbows with soap and water for at least 30 s.
- Dry hands and forearms up to the elbows completely with low-lint disposable towels or wipers.

The order of hand washing and garbing depends on the placement of the sink (see *4.4 Water Sources*). The order of garbing must be determined by the facility and documented in the facility's SOPs. Hands must be sanitized with alcohol-based hand rub before donning sterile gloves (see *Box 4*). Sterile gloves must be donned in a classified room or SCA.

Box 4. Hand Sanitizing Procedures

- Apply an alcohol-based hand rub to dry skin.
- Apply product to one hand and rub hands together, covering all surfaces of hands and fingers, until hands are dry.
- Allow hands to dry thoroughly before donning sterile gloves.

3.3 Garbing Requirements

Any person entering a compounding area where Category 1, Category 2, or Category 3 CSPs are prepared must be properly garbed. Garb must be donned and doffed in an order that reduces the risk of contamination. The required garb, manner of storage, and order of garbing must be determined by the facility and documented in the facility's SOPs. When preparing Category 2 or Category 3 CSPs, all garb should be donned in a classified area before entering the buffer room. If hand hygiene is completed outside of a classified area, alcohol-based hand rub must be used prior to donning garb. Skin must not be exposed inside the ISO Class 5 PEC (e.g., gloves must not be donned or doffed inside the ISO Class 5 PEC exposing bare hands). Donning and doffing garb should not occur in the same area at the same time. The minimum garbing requirements for preparing Category 1 and Category 2 CSPs include the following:

- Low-lint garment with sleeves that fit snugly around the wrists and an enclosed neck (e.g., gown or coverall)
- Low-lint covers for shoes
- Low-lint cover for head that covers the hair and ears, and if applicable, cover for facial hair
- Low-lint face mask
- Sterile powder-free gloves
- If using a RABS (i.e., a CAI or CACI), disposable gloves should be worn inside the gloves attached to the RABS sleeves. Sterile gloves must be worn over the gloves attached to the RABS sleeve

Garb must be replaced immediately if it becomes visibly soiled or if its integrity is compromised. Gowns and other garb must be stored in a manner that minimizes contamination (e.g., away from sinks to avoid splashing). If compounding Category 1 and Category 2 CSPs, gowns may be reused within the same shift by the same person if the gown is maintained in a classified area or adjacent to, or within, the SCA in a manner that prevents contamination. When personnel exit the compounding area, garb, except for gowns, cannot be reused and must be discarded or laundered before reuse. The facility's SOPs must describe disinfection procedures for reusing goggles, respirators, and other reusable equipment.

If the facility compounds Category 3 CSPs, additional garbing requirements must be continuously met in the buffer room in which Category 3 CSPs are prepared. The following additional garbing requirements must be followed in the buffer room where Category 3 CSPs are prepared for all personnel regardless of whether Category 3 CSPs are compounded on a given day:

1. Do not allow any exposed skin in the buffer room (i.e., face and neck must be covered).
2. All low-lint outer garb must be sterile, including the use of sterile sleeves over gauntlet sleeves when a RABS is used.
3. Disposable garbing items must not be reused, and laundered garb must not be reused without being laundered and resterilized with a validated cycle.
4. The facility's SOPs must describe disinfection procedures for reusing goggles, respirators, and other reusable equipment.

If compounding an HD, appropriate personal protective equipment (PPE) must be worn and disposed of in accordance with ⟨800⟩.

Gloves: Gloves must be sterile and powder free. Application of sterile 70% IPA to gloves must occur immediately before compounding and regularly throughout the compounding process.

All gloves must be inspected for holes, punctures, or tears and must be replaced immediately if such defects are detected.

The RABS sleeves and gloves and the pharmaceutical isolator sleeves and gloves should be changed per the manufacturer's recommendations and as defined in the facility's SOPs.

4. FACILITIES AND ENGINEERING CONTROLS

Sterile compounding facilities must be designed, outfitted, and maintained properly to minimize the risk of contamination of CSPs. The required air quality must be achieved and maintained through PECs and secondary engineering controls (SECs). The anteroom, buffer room, and SCA must be separated from areas not directly related to compounding. The anteroom and buffer room must be appropriately controlled to achieve and maintain the required air quality classifications. The design of the facility should take into account the number of personnel and their movements, and the impact the placement of equipment, supplies, and components could have on the maintenance of air quality. The number of operations being performed, the equipment (e.g., PECs, carts, computers), the personnel in the compounding area (and in adjacent areas), and the complexity of the compounding procedures are critical considerations for maintaining control of environmental conditions in the facility.

4.1 Protection from Airborne Contaminants

Sterile compounding facilities must be designed to minimize the risk of airborne contamination of the area in which sterile compounding occurs. Proper design and controls are required to minimize the risk of exposure of CSPs to airborne contaminants.

4.1.1 Air quality standards: The ISO standards for air quality in controlled environments are provided in *Table 4* and referenced throughout this chapter.

Table 4. ISO Classification of Particulate Matter in Room Air[a]

ISO Class	Particle Count per Cubic Meter[b]
3	35.2
4	352
5	3520
6	35,200
7	352,000
8	3,520,000

[a] Adapted from ISO 14644-1, Cleanrooms and associated controlled environments—Part 1: Classification of air cleanliness by particle concentration.
[b] Limits for number of particles ≥0.5 µm measured under dynamic operating conditions.

4.1.2 Design requirements to maintain air quality: Facilities used for compounding CSPs must be designed so that air quality improves with movement through separate operational areas to the PEC. Classified areas in which the air quality is controlled (see *Table 4*) include anterooms, buffer rooms, and PECs.

- Anterooms providing access only to positive-pressure buffer rooms must meet at least ISO Class 8 classification. Anterooms providing access to negative-pressure buffer rooms must meet at least ISO Class 7 classification (see ⟨800⟩). Typically, personnel hand hygiene and garbing procedures, staging of components, and other activities that potentially generate higher levels of particulates are performed in the anteroom. Anterooms are also transition areas to ensure that proper air classification and pressure relationships are maintained between classified and unclassified areas.
- A buffer room must meet at least ISO Class 7 air quality. Activities in the buffer room must be controlled to minimize any effects on air quality in the area where CSPs are prepared.
- Category 1, Category 2, and Category 3 CSPs must be compounded in an ISO Class 5 or better PEC. If compounding only Category 1 CSPs, the PEC may be placed in an unclassified SCA.

4.2 Facility Design and Environmental Controls

In addition to minimizing airborne contamination, sterile compounding facilities must be designed and controlled to provide a well-lighted and comfortable working environment (see *Physical Environments That Promote Safe Medication Use* ⟨1066⟩). The cleanroom suite should be maintained at a temperature of 20° or cooler and a relative humidity of 60% or below to minimize the risk of microbial proliferation and to provide comfortable conditions for compounding personnel attired in the required garb. The temperature and humidity must be monitored in each room of the cleanroom suite each day that compounding is performed, either manually or by a continuous recording device. The results of the temperature and humidity readings must be documented at least once daily or stored in the continuous recording device and must be retrievable. The temperature and humidity readings must be reviewed as described in the facility's SOPs. Temperature and humidity in the cleanroom suite must be controlled through a heating, ventilation, and air conditioning (HVAC) system. Free-standing air conditioners, humidifiers, and dehumidifiers must not be used within the classified area or the SCA. Temperature and humidity monitoring devices must be verified for accuracy at least every 12 months or as required by the manufacturer.

The designated person(s) is responsible for ensuring that each area related to CSP preparation meets the classified air quality standard appropriate for the activities to be conducted in that area. The designated person(s) must also ensure that the ISO Class 5 areas are located, operated, maintained, monitored, and certified to have appropriate air quality.

4.2.1 Types of SECs and design: The PEC must be located in the buffer room of the cleanroom suite or the SCA in a manner that minimizes conditions that could increase the risk of microbial contamination. For example, strong air currents from opened doors, personnel traffic, or air streams from the HVAC system(s) can disrupt the unidirectional airflow of an open-faced PEC such as a laminar airflow workbench (LAFW). Access to the SEC must be restricted to authorized personnel and required materials.

Cleanroom suite: The ISO-classified anteroom and buffer room must be separated from the surrounding unclassified areas of the facility by fixed walls and doors, and controls must be in place to minimize the flow of lower-quality air into the more controlled areas. The classified rooms must be equipped with a pressure-differential monitoring system. Air supplied to the cleanroom suite must be introduced through HEPA filters that are located in the ceiling of the buffer room and anteroom.

Air returns in the cleanroom suite must be low on the wall unless a visual smoke study demonstrates an absence of stagnant airflow. This smoke study along with environmental monitoring must be repeated whenever a change is made to the placement of equipment within the room or any other alteration is performed within the cleanroom suite that affects the quality of the air (e.g., HVAC alterations, change of HEPA filter units).

The anteroom must have a line of demarcation to separate the clean side from the dirty side. The anteroom is entered through the dirty side, and the clean side is the area closest to the buffer room. Alternatively, facilities may be designed with two separate anterooms—a dirty anteroom and a clean anteroom. The anteroom is entered through the dirty anteroom, and the clean anteroom is the area closest to the buffer room.

It is also critical to control materials (e.g., supplies and equipment) as they move from classified areas of lower quality to those of higher quality (e.g., from an ISO Class 8 anteroom to an ISO Class 7 buffer room to an ISO Class 5 PEC) to minimize the influx of contaminants. Airlocks and interlocking doors may be used to facilitate better control of air balance between areas of differing ISO classification (e.g., between the buffer room and anteroom) or between a classified area and an unclassified area (e.g., between the anteroom and a hallway). If a pass-through chamber is used, both doors must never be opened at the same time, and doors should be interlocking.

Due to the interdependence of the various rooms or areas that make up a sterile compounding facility, it is essential to carefully define and control the dynamic interactions permitted between areas and rooms. Consider the placement of door closures, door surfaces, and the movement of the doors, all of which can affect airflow. Seals and sweeps should not be installed at doors between buffer rooms and anterooms. Access doors should be hands-free. Tacky mats must not be placed within ISO-classified areas. If compounding both sterile and nonsterile preparations (e.g., presterilization procedures), the respective PECs must be placed in separate rooms unless those PECs are sufficiently effective that the room can continuously maintain ISO Class 7 classification. If the PECs used for sterile and nonsterile compounding are placed in the same room, they must be placed at least 1 m apart, and particle-generating activity must not be performed when sterile compounding is in process.

Segregated compounding area (SCA): A PEC may be located within an unclassified area without an anteroom or buffer room. This type of design is called an SCA. Only Category 1 CSPs may be compounded in an SCA. The SCA must be located away from unsealed windows, doors that connect to the outdoors, and traffic flow, all of which may adversely affect the air quality in the PEC. An SCA must not be located where environmental control challenges (e.g., restrooms, warehouses, or food preparation areas) could negatively affect the air quality of the PEC within the SCA. The impact of activities (e.g., patient care activities) that will be conducted around or adjacent to the SCA must be considered carefully when designing such an area. The area within 1 m of the PEC should be dedicated only for sterile compounding (e.g., not storage, hand hygiene, donning and doffing garb, or other highly particle-generating activities such as patient care).

4.2.2 The CSP compounding environment: The PEC must be certified to meet ISO Class 5 or better conditions (see *Table 4*) during dynamic operating conditions and must be designed to minimize the risk of contamination during compounding of CSPs.

Unidirectional airflow must be maintained in the PEC. HEPA-filtered air must be supplied by the PEC at a velocity sufficient to sweep particles away from critical sites and maintain unidirectional airflow during operations. Proper design, control, and use minimizes turbulence and creation of eddies or stagnant air in the PEC.

4.2.3 Types of PECs and placement: Proper placement of the PEC is critical to ensuring an ISO Class 5 environment for preparing CSPs. Placement of the PEC must allow for cleaning around the PEC. See *Table 5* for a summary of minimum requirements for the placement of PECs for preparing non-HD CSPs.

Types of PECs and their placement include the following:

Laminar airflow system (LAFS): An LAFS provides an ISO Class 5 or better environment for sterile compounding. The LAFS provides unidirectional HEPA-filtered airflow that is designed to minimize the risk of contamination of a sterile compounding environment. The unidirectional airflow within the LAFS helps protect the direct compounding area (DCA) from process-generated contamination (e.g., opening wrappings of sterile containers, compounder movement) as well as from outside sources.

Types of LAFS and their placement include the following:

Laminar airflow workbench (LAFW): An LAFW is a device that provides an ISO Class 5 or better environment for sterile compounding. The LAFW provides either horizontal or vertical unidirectional HEPA-filtered airflow. [NOTE—An LAFW must not be used for preparation of antineoplastic and/or active pharmaceutical ingredient (API) HDs (see ⟨800⟩).]

Integrated vertical laminar flow zone (IVLFZ): An IVLFZ is a designated ISO Class 5 area serving as the PEC within an ISO Class 7 or cleaner buffer room. In the IVLFZ, unidirectional airflow is created by placing HEPA filters over the entire surface of the worktables and by effective placement of air returns. The unidirectional HEPA-filtered zone must be separated from the ISO Class 7 area with a physical barrier to direct the airflow downward over the work area to separate the DCA from potential sources of contamination. Strategic location of air returns in addition to full coverage of HEPA filters above the work surface is required. Both static and dynamic smoke studies verifying a continuous flow of HEPA-filtered air void of turbulence, dead air zones, and refluxing from the HEPA filters to and across the entire work area and to the air returns must be documented (e.g., with video). [NOTE—Dynamic airflow smoke pattern tests have shown that it is difficult to achieve this type of design and also achieve and maintain unidirectional airflow under dynamic operating conditions.]

[NOTE—An IVLFZ must not be used for preparation of antineoplastic and/or API HDs (see ⟨800⟩).]

Class II biological safety cabinet (BSC): A Class II BSC is a ventilated cabinet with an open front and inward and downward unidirectional HEPA-filtered airflow and HEPA-filtered exhaust. The BSC is designed to provide worker protection from exposure to airborne drugs and to provide an ISO Class 5 or better environment for preparing CSPs. [NOTE—The exhaust air from the BSC must be externally vented for preparation of antineoplastic and/or API HDs (see ⟨800⟩).]

Placement of LAFS: The LAFS must be located out of traffic patterns and away from room air currents that could disrupt the intended airflow patterns inside the PEC. If used to prepare only Category 1 CSPs, the ISO Class 5 PEC may be located in an unclassified SCA. If used to prepare Category 2 or Category 3 CSPs, the LAFS must be located within a cleanroom suite with an ISO Class 7 or better buffer room with an ISO Class 8 or better anteroom. A dynamic airflow smoke pattern test must be performed in the PEC initially and at least every 6 months to ensure that 1) the LAFS is properly placed into the facility and 2) compounders understand how to utilize the unidirectional airflow to maintain first air in the DCA.

Restricted-access barrier system (RABS): A RABS is an enclosure that provides HEPA-filtered ISO Class 5 unidirectional air. It allows for the ingress and/or egress of materials through defined openings that have been designed and validated to preclude the transfer of environmental air contamination and are generally not to be opened during compounding operations. RABS include compounding aseptic isolators (CAIs) and compounding aseptic containment isolators (CACIs). In a CAI or CACI, glove ports are used to provide physical separation between the surrounding area and the aseptic manipulations.

Compounding aseptic isolator: A CAI is designed for compounding non-HD CSPs. It is designed to maintain an ISO Class 5 environment throughout the compounding and material transfer processes. Air exchange into the

CAI from the surrounding environment must not occur unless the air has first passed through a HEPA filter. [NOTE—A CAI must not be used for preparation of antineoplastic and/or API HDs (see ⟨800⟩).]

Compounding aseptic containment isolator: A CACI is designed to provide worker protection from exposure to undesirable levels of airborne drug throughout the compounding and material transfer processes and to maintain an ISO Class 5 environment for compounding sterile HD preparations (see ⟨800⟩).

Placement of RABS: If used to prepare only Category 1 CSPs, the ISO Class 5 environment may be achieved by placing the RABS in an unclassified SCA. If used to prepare Category 2 or Category 3 CSPs, the RABS must be located within a cleanroom suite with an ISO Class 7 or better buffer room with an ISO Class 8 or better anteroom. For placement of a CACI used for the preparation of antineoplastic and/or API HDs, see ⟨800⟩.

When a RABS is used, the recovery time after opening the transfer chamber to achieve ISO Class 5 air quality must be documented (e.g., by the manufacturer), and internal procedures must be developed to ensure that adequate recovery time is allowed after opening and closing the RABS, both before and during compounding operations. A dynamic airflow smoke pattern test must be performed in the PEC under dynamic operating conditions initially and at least every 6 months to ensure that 1) the RABS is properly integrated into the facility and 2) compounders understand how to utilize the unidirectional airflow to maintain first air in the DCA.

Pharmaceutical isolator: A pharmaceutical isolator provides isolation from the surrounding area and maintains ISO Class 5 air quality during dynamic operating conditions. [NOTE—A CAI or CACI is not a pharmaceutical isolator.] A pharmaceutical isolator comprises four elements:

1. Controlled workspace
2. Transfer device(s)
3. Access device(s)
4. Integral decontamination system

Placement of pharmaceutical isolators: A pharmaceutical isolator used to prepare only Category 1 CSPs can be placed in an unclassified SCA. If the pharmaceutical isolator is used to prepare Category 2 or Category 3 CSPs, the pharmaceutical isolator must be placed in an ISO Class 8 or better room. [NOTE—An anteroom is not required when using a pharmaceutical isolator.] A dynamic airflow smoke pattern test must be performed in the PEC initially and at least every 6 months to ensure that 1) the pharmaceutical isolator is properly placed in the facility and 2) compounders understand how to utilize the unidirectional airflow to maintain first air in the work zone.

Table 5. Summary of Minimum Requirements for Placement of PECs for Compounding Non-HD CSPs[a]

PEC Type	Device Type	Placement for Compounding Only Category 1 CSPs	Placement for Compounding Category 2 and 3 CSPs
LAFS	LAFW	Unclassified SCA	ISO Class 7 positive-pressure buffer room with an ISO Class 8 positive-pressure anteroom
	IVLFZ	N/A[b]	ISO Class 7 positive-pressure buffer room with an ISO Class 8 positive-pressure anteroom
	BSC	Unclassified SCA	ISO Class 7 positive-pressure buffer room with an ISO Class 8 positive-pressure anteroom
RABS	CAI or CACI	Unclassified SCA	ISO Class 7 positive-pressure buffer room with an ISO Class 8 positive-pressure anteroom
Pharmaceutical isolator	Pharmaceutical isolator	Unclassified SCA	ISO Class 8 positive-pressure room

[a] For compounding HDs, see ⟨800⟩.
[b] An IVLFZ must not be used in an unclassified area.

If a robotic enclosure is used as the PEC, or placed within the PEC, a dynamic airflow smoke pattern test must be performed initially and at least every 6 months thereafter to ensure that 1) it is properly integrated into the facility, 2) there is no turbulence or refluxing at any critical site(s), 3) room air does not enter the PEC where sterile products and/or preparations may be exposed, and 4) all processes can be performed without introducing contamination to the DCA(s).

4.2.4 Air exchange requirements: For cleanroom suites, adequate HEPA-filtered airflow to the buffer room(s) and anteroom(s) is required to maintain the appropriate ISO classification during compounding activities. Airflow is measured in terms of the number of air changes per hour (ACPH). The ACPH may need to be higher to maintain the required ISO classification and microbial state of control depending on the following factors:

- Number of personnel permitted to work in the area
- Number of particles that may be generated from activities and processes in the area
- Equipment located in the room
- Room pressure

See *Table 6* for a summary of ACPH requirements for non-HD sterile compounding areas. Additional ACPH requirements include:

A minimum of 30 total HEPA-filtered ACPH must be supplied to ISO Class 7 rooms:

- The total HEPA-filtered air change rate must be adequate to maintain ISO Class 7 during dynamic operating conditions considering the factors listed above

- At least 15 ACPH of the total air change rate in a room must come from the HVAC through HEPA filters located in the ceiling
- The HEPA-filtered air from the PEC, when added to the HVAC-supplied HEPA-filtered air, must increase the total HEPA-filtered ACPH to at least 30 ACPH
- If the PEC is used to meet the minimum total ACPH requirements, the PEC must not be turned off except for maintenance
- Rooms where activity levels are high may require more HEPA-filtered ACPH to maintain ISO Class 7 air quality under dynamic operating conditions
- The ACPH from HVAC, ACPH contributed from the PEC, and the total ACPH must be documented on the certification report

A minimum of 20 total HEPA-filtered ACPH must be supplied to ISO Class 8 rooms:

- The total HEPA-filtered air change rate must be adequate to maintain ISO Class 8 under dynamic operating conditions considering the factors listed above
- At least 15 ACPH of the total air change rate in a room must come from the HVAC through HEPA filters located in the ceiling
- Rooms where activity levels are high may require more HEPA-filtered ACPH to maintain ISO Class 8 air quality under dynamic operating conditions
- The total ACPH must be documented on the certification report

Table 6. Summary of ACPH Requirements for Non-HD Sterile Compounding Areas

Compounding Area	ACPH Requirement
Unclassified SCA	No requirement
ISO Class 7 room(s)	≥30 ACPH
ISO Class 8 room(s)	≥20 ACPH

4.2.5 Establishing and maintaining pressure differentials: Continuous differential positive pressure is required to minimize airflow from an area with lower air-quality classification to an area of higher air-quality classification. In a cleanroom suite, a minimum differential positive pressure of 0.020-inch water column is required between adjacent ISO-classified areas (e.g., between the buffer room and anteroom). The pressure differential between the anteroom and the unclassified area must not be less than 0.020-inch water column. No pressure differential is required between the SCA and the surrounding area. See ⟨800⟩ for pressure requirements for compounding HD CSPs.

Where pressure differentials are required, a pressure differential monitoring device must be used to continuously monitor the pressure differentials. The quantitative results from the pressure monitoring device must be reviewed and documented at least daily on the days when compounding is occurring.

4.2.6 Facilities preparing Category 2 or Category 3 CSPs from nonsterile starting components: Weighing, measuring, or otherwise manipulating components could generate airborne chemical particles (e.g., API or added substances). If preparing Category 2 or Category 3 CSP from nonsterile component(s), presterilization procedures, such as weighing and mixing, must be completed in an ISO Class 8 or better environment (e.g., anteroom or buffer room). Presterilization procedures must be performed in single-use containment glove bags, containment ventilated enclosures (CVEs), BSCs, or CACIs to minimize the risk of airborne contamination. CVEs, BSCs, or CACIs used for presterilization procedures must be certified at least every 6 months.

Presterilization procedures must not adversely affect the required air quality of the SEC as demonstrated during certification under dynamic operating conditions. Personnel must follow the hygiene and garbing requirements as described in *3. Personal Hygiene and Garbing* during presterilization procedures.

4.3 Creating Areas to Achieve Easily Cleanable Conditions

4.3.1 Cleanroom suite: The surfaces of ceilings, walls, floors, doors, door frames, fixtures, shelving, work surfaces, counters, and cabinets in the classified area must be smooth, impervious, free from cracks and crevices, and nonshedding so they can be cleaned and disinfected and to minimize spaces in which microorganisms and other contaminants can accumulate. Surfaces should be resistant to damage (e.g., rust) by cleaning agents, sporicidal and other types of disinfectants, and tools used to clean. Junctures between the ceiling and the walls and between the walls and the floor must be sealed to eliminate cracks and crevices where dirt can accumulate. If ceilings consist of inlaid panels, the panels must be caulked around each panel to seal them to the support frame.

Walls must be constructed of, or may be covered with, durable material (e.g., epoxy painted walls or heavy-gauge polymer) and the integrity of the surface must be maintained. Panels must be joined together and sealed to each other and the support structure. Floors must include coving to the sidewall, or the juncture between the floor and the wall must be caulked. Classified areas should minimize dust-collecting overhangs, such as utility pipes, and ledges, such as windowsills. If overhangs or ledges are present, they must be easily cleanable. The exterior lens surface of ceiling light fixtures must be smooth, mounted flush, and sealed. Any other penetrations through the ceiling or walls must be sealed.

4.3.2 SCA: The SCA and all surfaces (e.g., walls, floors, counters, and equipment) in the SCA must be clean, uncluttered, and dedicated to compounding. Surfaces in the SCA should be smooth, impervious, free from cracks and crevices, and non-shedding so they can be easily cleaned and disinfected and to minimize spaces in which microorganisms and other contaminants can accumulate. Surfaces should be resistant to damage (e.g., rust) by cleaning agents, sporicidal and other types of disinfectants, and tools used to clean. Dust-collecting overhangs, such as utility pipes, and ledges, such as windowsills, should be minimized. If overhangs or ledges are present, they must be easily cleanable.

4.4 Water Sources

The facility where CSPs are prepared must be designed so that activities such as hand hygiene and garbing will not adversely affect the ability of the PEC to function as designed. Sinks should enable hands-free use. Surfaces of the sink(s) must be cleaned and disinfected each day of use, and a sporicidal disinfectant must be applied at least monthly (see *7.1 Agents and Supplies for Cleaning, Disinfecting, and Applying Sporicidal Disinfectants*).

In facilities with a cleanroom suite, the sink used for hand hygiene may be placed either inside or outside of the anteroom. If the sink is located outside of the anteroom, it must be located in a clean space to minimize the risk of bringing contaminants into the anteroom. If the sink is located inside the anteroom, it may be placed on either the clean side or the dirty side of the anteroom. [NOTE—The order of hand washing and garbing depends on the placement of the sink (see *3.2 Hand Hygiene* and *3.3 Garbing Requirements*)] . The buffer room must not contain plumbed water sources [e.g., sink(s), eyewash(es), shower(s), or floor drain(s)]. The anteroom must not contain floor drain(s). If installed, sprinkler systems should be recessed and covered, and the covers should be easily cleanable.

In a facility with an SCA design, a hand-washing sink must be placed not closer than 1 m to the PEC and may be either inside the SCA or in close proximity to the SCA.

4.5 Placement and Movement of Materials

Only furniture, equipment, and other materials necessary for performing compounding activities are permitted in a classified area or SCA, and they should be low-shedding and easily cleaned and disinfected. Their number, design, location, and manner of installation must not impact environmental air quality and must promote effective cleaning and disinfecting. No shipping carton(s) or other corrugated or uncoated cardboard are allowed in a classified area or SCA.

Carts used to transport components or equipment into classified areas must be constructed from nonporous materials with cleanable casters and wheels to promote mobility and ensure ease of cleaning and disinfection. In a cleanroom suite, carts must not be moved from the dirty side to the clean side of the anteroom unless the entire cart, including casters, is cleaned and disinfected.

Only equipment necessary for performing compounding activities is permitted in the PEC. Proper placement of equipment in a PEC must be initially verified by a dynamic airflow smoke pattern test to demonstrate minimal disruption in airflow. The dynamic airflow smoke pattern test must be repeated if equipment is placed in a different location. Equipment and other items used in a classified area or SCA should not be removed except for calibration, servicing, cleaning, or other activities associated with maintenance. If removed, these items must be cleaned and wiped with sterile 70% IPA or a suitable disinfectant before they are returned to the classified area or the SCA.

Materials necessary for performing compounding activities that have been exposed in patient care and treatment areas must not enter anterooms, buffer rooms, or segregated compounding areas unless thoroughly cleaned and disinfected. The designated person(s) is responsible for addressing other areas of risk in the facility's SOPs. The designated person(s) may permit accommodations as long as the quality of the CSP and environment will not be affected. Accommodations must be documented.

5. CERTIFICATION AND RECERTIFICATION

Before a compounding area is used to compound either Category 1, Category 2, or Category 3 CSPs, it must be independently certified using the requirements in this chapter and when applicable, manufacturer specifications. Certification indicates that the compounding area is meeting its design and air quality specifications (see *Table 4*).

Certification of the classified areas including the PEC must be performed initially, and recertification must be performed at least every 6 months and must include:

- *Airflow testing:* Airflow testing is performed to determine acceptability of the air velocity, the room air exchange rate, and the room pressure differential in doorways between adjacent rooms to ensure consistent airflow and that the appropriate quality of air is maintained under dynamic operating conditions. The ACPH from HVAC, ACPH contributed from the PEC, and the total ACPH must be documented on the certification report.
- *HEPA filter integrity testing:* HEPA filters must be leak tested at the factory and then leak tested again after installation and as part of recertification.
- *Total particle count testing:* (See *5.1 Total Airborne Particle Sampling*.) Total particle count testing must be performed under dynamic operating conditions using calibrated electronic equipment.
- *Dynamic airflow smoke pattern test:* Smoke pattern tests must be performed for each PEC during dynamic operating conditions to demonstrate unidirectional airflow and sweeping action over and away from the preparation(s).

Classified areas additionally must be recertified if there are changes to the area such as redesign, construction, replacement or relocation of any PEC, or alteration in the configuration of the room that could affect airflow or air quality.

All certification and recertification records must be reviewed by the designated person(s) to ensure that the classified environments meet the minimum requirements in this chapter. The number of personnel present in each PEC and SEC during total particle-count tests and dynamic airflow smoke-pattern tests must be documented. Records must be maintained in accordance with the requirements in *20. Documentation*.

A corrective action plan must be implemented and documented in response to any out-of-range results. Data collected in response to corrective actions must be reviewed to confirm that the actions taken have been effective.

5.1 Total Airborne Particle Sampling

The engineering control equipment function must function as designed to ensure that the levels of total airborne particles remain within acceptable limits during compounding (see *Table 4*). Total airborne particle count testing must be conducted in all classified areas during dynamic operating conditions at least every 6 months to measure the performance of the engineering controls that are being used to provide the specified levels of air cleanliness (e.g., in the ISO Class 5 PEC and ISO Class 7 and 8 rooms).

Total airborne particle sampling sites must be selected in all classified areas. Measurements of total airborne particles must be taken in each PEC at locations where there is greatest risk to the exposed CSPs, containers, and closures. When conducting sampling of the PEC, care should be taken to avoid disturbing the unidirectional airflow within the PEC. All sampling sites and procedures must be described in the facility's SOPs. Measurements of total airborne particles in other

classified areas, including the buffer room(s) and anteroom(s), should be taken at representative locations that reflect the quality of air in the room(s).

Data evaluation and action levels: If levels measured during the total air sampling program exceed the criteria in *Table 4* for the ISO classification of the area sampled, the cause must be investigated and corrective action taken and documented. Data collected in response to corrective actions must be reviewed to confirm that the actions taken have been effective. Some examples of corrective action include process or facility improvements or HEPA filter replacement or repair. The extent of the investigation should be consistent with the deviation and should include an evaluation of trends.

6. MICROBIOLOGICAL AIR AND SURFACE MONITORING

An effective microbiological air and surface monitoring program provides information on the environmental quality of the compounding area. In addition, an effective microbiological air and surface monitoring program identifies environmental quality trends over time, identifies potential routes of contamination, and allows for implementation of corrective actions to minimize the risk of CSP contamination. Sterile compounding facilities must develop and implement written procedures for microbiological air and surface monitoring (see *17. SOPs*). All microbiological air and surface monitoring procedures, the test results, and the corrective actions must be documented, and the records must be maintained in accordance with the requirements in *20. Documentation*. Data collected in response to corrective actions must be reviewed to confirm that the actions taken have been effective.

6.1 General Monitoring Requirements

The microbiological air and surface monitoring program must include 1) viable impact volumetric airborne particulate sampling and 2) surface sampling. The goals of a microbiological air and surface monitoring program are to determine whether contamination is present at unacceptable levels and to assess whether proper personnel practices are being followed, cleaning and disinfecting agents are effective, and environmental quality is maintained.

The microbiological air and surface monitoring program involves the collection and evaluation of samples from various air and surface locations to detect airborne and surface contaminants. The data from microbiological airborne and surface sampling are then used to assess risks for contamination, potential routes of contamination, and the adequacy of cleaning and disinfecting agents and procedures. Regular review of the sampling data must be performed to detect trends and the results of the review must be documented.

In addition, results from microbiological air and surface sampling must be reviewed in conjunction with personnel data (i.e., training records, visual observations, competency assessments) to assess the state of control and to identify potential risks of contamination. Corrective action in response to any adverse findings is required to maintain the necessary environmental quality for preparation of CSPs. Data must also be reviewed following corrective actions to confirm that the actions taken have been effective in achieving the required microbiological air and surface quality levels (see *Table 4*, *Table 7*, and *Table 8*).

Microbiological air and surface monitoring must be performed initially for sterile compounding facilities to establish a baseline level of environmental quality. After initial sampling, the environment in which sterile compounding activities are performed must be monitored according to the minimum frequencies described in this section to ensure that the environment remains suitable for sterile compounding.

Evaluating results collected over a period of time can be useful in identifying trends or determining that a significant change has occurred, even when the results fall within the specified levels.

Microbiological air and/or surface monitoring must be conducted in all classified areas during dynamic operating conditions to confirm that the required environmental quality is maintained. In addition to the specific sampling frequencies described in this section, sampling must be performed in the following circumstances:

- In conjunction with the certification of new facilities and equipment
- After any servicing of facilities or equipment (see *4. Facilities and Engineering Controls*)
- In response to identified problems (e.g., positive growth in sterility tests of CSPs)
- In response to identified trends (e.g., repeated positive gloved fingertip and thumb sampling results, failed media fill testing, or repeated observations of air or surface contamination)
- In response to changes that could impact the sterile compounding environment (e.g., change in cleaning agents)

The microbiological air and surface monitoring program must be clearly described in the facility's SOPs, which must include a diagram of the sampling locations, procedures for collecting samples, frequency of sampling, size of samples (e.g., surface area, volume of air), time of day of sampling in relation to activities in the compounding area, and action levels that will trigger corrective action.

The times and locations of sampling should be carefully selected based on their relationship to the activities performed in the area. It is important to obtain samples from locations that pose the highest possible risk of contamination to the CSP and that are likely to be representative of the conditions throughout the area. To obtain air and surface samples that are representative of the typical compounding conditions at the facility, in all PECs and classified rooms, air sampling must be conducted during dynamic operating conditions and surface sampling should be performed at the end of a compounding activity or shift but before the area has been cleaned and disinfected. The monitoring program must be designed and conducted in a manner that minimizes the chance that the sampling itself will contribute to contamination of the CSP or the environment.

It is important that personnel are trained and competent in air and surface sampling procedures to ensure accurate and reproducible sampling. All impaction air samplers must be serviced and calibrated as recommended by the manufacturer.

6.2 Monitoring Air Quality for Viable Airborne Particles

A monitoring program for viable airborne particles must be developed and implemented to assess microbiological air quality in all classified areas.

6.2.1 Viable air sampling—timing and locations: Volumetric active air sampling of all classified areas using an impaction air sampler must be conducted in each classified area [e.g., ISO Class 5 PEC and ISO Class 7 and 8 room(s)] during dynamic operating conditions. For entities compounding Category 1 and Category 2 CSPs, this must be completed at least every 6 months. For entities compounding any Category 3 CSPs, this must be completed within 30 days prior to the commencement of any Category 3 compounding and at least monthly thereafter regardless of the frequency of compounding Category 3 CSPs. Air sampling sites must be selected in all classified areas.

6.2.2 Viable air sampling procedures: When conducting sampling of the PEC, care should be taken to avoid disturbing unidirectional airflow. See *Box 5* for active air sampling procedures. A general microbiological growth media that supports the growth of bacteria and fungi must be used (e.g., TSA). COAs from the manufacturer must verify that the sampling media devices meet the expected growth promotion, pH, and sterilization requirements. Samples must be incubated in an incubator at the temperatures listed in *Box 5*. The incubator temperature must be monitored during incubation, either manually or by a continuous recording device, and the results must be reviewed and documented as described in the facility's SOPs. The incubator must be placed in a location outside of the sterile compounding area.

Box 5. Active Air Sampling Procedures for Viable Airborne Monitoring

1. Follow the manufacturer's instructions for operation of the impaction air sampler, including placement of media device(s).
2. Using the impaction air sampler, test at least 1 cubic meter or 1000 L of air from each location sampled.
3. At the end of each sampling period, retrieve the media device and cover it. Handle and store media devices to avoid contamination and prevent condensate from dropping onto the agar during incubation and affecting the accuracy of the cfu reading (e.g., invert plates).
4. Incubate the media device at 30°–35° for no less than 48 h. Examine for growth. Record the total number of discrete colonies of microorganisms on each media device as cfu per cubic meter of air on an environmental sampling form based on sample type (i.e., viable air), sample location, and sample date.
5. Then incubate the media device at 20°–25° for no less than 5 additional days. Examine for growth. Record the total number of discrete colonies of microorganisms on each media device as cfu per cubic meter of air on an environmental sampling form based on sample type (i.e., viable air), sample location, and sample date.
6. Alternatively, to shorten the overall incubation period, two sampling media devices may be collected for each sample location and incubated concurrently.
   A. Both media devices could be TSA or one media device could be TSA and the other fungal media (e.g., malt extract agar [MEA] or Sabouraud dextrose agar [SDA]).
   B. Incubate each media device in a separate incubator. Incubate one media device at 30°–35° for no less than 48 h, and incubate the other media device at 20°–25° for no less than 5 days. If fungal media are used as one of the samples, incubate the fungal media sample at 20°–25° for no less than 5 days.
   C. Count the total number of discrete colonies of microorganisms on each media device, and record these results as cfu per cubic meter of air.
   D. Record the results of the sampling on an environmental sampling form based on sample type (i.e., viable air), and include the sample location and sample date.

6.2.3 Viable air sampling data evaluation and action levels: Evaluate cfu counts against the action levels in *Table 7* and examine counts in relation to previous data to identify adverse results or trends. If two sampling media devices are collected at a single location, all recovered growth on each must be documented and action levels applied to each sampling media device separately. If levels measured during the viable air monitoring program exceed the levels in *Table 7* for the ISO classification levels of the area sampled, the cause must be investigated and corrective action must be taken. Data collected in response to corrective actions must be reviewed to confirm that the actions taken have been effective. The corrective action plan must be dependent on the cfu count and the microorganism recovered. Some examples of corrective action include process or facility improvements, personnel training, cleaning and disinfecting, or HEPA filter repair and/or replacement. The extent of the investigation should be consistent with the deviation and should include an evaluation of trends. The corrective action plan must be documented and should include resampling of failed areas to confirm corrective action was successful. If levels measured during viable air sampling exceed the levels in *Table 7*, an attempt must be made to identify any microorganisms recovered to the genus level (see *Microbial Characterization, Identification, and Strain Typing* ⟨1113⟩) with the assistance of a microbiologist.

Table 7. Action Levels for Viable Airborne Particle Air Sampling

ISO Class	Air Sampling Action Levels [cfu/cubic meter (1000 liters) of air/media device]
5	>1
7	>10
8	>100

6.3 Monitoring Surfaces for Viable Particles

Surface sampling is an important tool used to assist in maintenance of a suitably controlled environment for compounding CSPs. Surface sampling is useful for evaluating facility cleaning and material handling procedures, work surface cleaning and disinfecting procedures, and personnel competency in work practices such as cleaning and disinfecting. All sampling sites and procedures must be described in the facility's SOPs.

6.3.1 Surface sampling—timing and locations: Each classified area, including each room and the interior of each ISO Class 5 PEC and pass-through chambers connecting to classified areas, must be sampled for microbial contamination using a risk-based approach. Samples should be taken from the following classified areas:

- Equipment contained within the PEC
- Staging or work area(s) near the PEC
- Frequently touched surfaces

Surface sampling in the DCA must also be conducted in conjunction with media-fill testing to assess aseptic manipulation competency (see *2.3 Competency Testing in Aseptic Manipulation*)

When conducted, surface sampling should be performed at the end of a compounding activity or shift but before the area has been cleaned and disinfected.

For entities compounding Category 1 and Category 2 CSPs, surface sampling of all classified areas, and pass-through chambers connecting to classified areas, must be conducted at least monthly (see *Microbiological Control and Monitoring of Aseptic Processing Environments* ⟨1116⟩).

For entities compounding any Category 3 CSPs, surface sampling of all classified areas, and pass-through chambers connecting to classified areas, must be completed prior to assigning a BUD longer than the limits established in *Table 13*, and at least weekly (see ⟨1116⟩) on a regularly scheduled basis regardless of the frequency of compounding Category 3 CSPs. Additionally, surface sampling must be conducted within the PEC used to prepare Category 3 CSPs, at the end of each batch before cleaning and disinfection occurs, unless a self-enclosed robotic device is used. When a self-enclosed robotic device is used as the PEC to prepare Category 3 CSPs, surface sampling must be conducted at least once daily at the end of compounding operations, before cleaning and disinfection occurs.

6.3.2 Surface sampling procedures: See *Box 6* for the procedures for surface sampling on flat surfaces. Surface sampling media devices (e.g., plates, paddles, or slides) containing microbial growth media must be used for sampling flat surfaces. COAs from the manufacturer must verify that the sampling media devices meet the expected growth promotion, pH, and sterilization requirements. Surface sampling media devices must contain general microbial growth media (e.g., TSA) supplemented with neutralizing additives (e.g., lecithin and polysorbate 80) to neutralize the effects of any residual disinfecting agents. Surface sampling media devices must have a raised convex surface. Sterile swabs wetted with sterile water or a sterile neutralizing buffer may be used when sampling irregular surfaces and difficult-to-reach locations such as crevices, corners, and spaces between surfaces. After sampling, the sampled area must be thoroughly cleaned and disinfected (see *7. Cleaning, Disinfecting, and Applying Sporicidal Disinfectants and Sterile 70% IPA*).

Samples must be incubated in an incubator at the temperatures listed in *Box 6*. The incubator temperature must be monitored during incubation, either manually or by a continuous recording device, and the results must be reviewed and documented. The incubator must be placed in a location outside of the sterile compounding area.

Box 6. Surface Sampling Procedures

1. Remove the cover from the surface sampling media device. Using a rolling motion, firmly press the media surface onto the surface to be sampled. The media device will leave a residue of growth media on the sample site. After sampling, clean and disinfect the sampled area to remove the residue from the surface.
2. Cover each media device. Handle and store media devices to avoid contamination and prevent condensate from dropping onto the agar during incubation and affecting the accuracy of the cfu reading (e.g., invert plates).
3. Incubate media device(s) at 30°–35° for no less than 48 h. Examine for growth. Record the total number of discrete colonies of microorganisms on each media device as cfu per media device on an environmental sampling form based on sample type (i.e., surface), sample location, and sample date.
4. Incubate the media device at 20°–25° for no less than 5 additional days. Examine for growth. Record the total number of discrete colonies of microorganisms on each media device (cfu per sample) on the environmental sampling record based on sample type (i.e., surface), sample location, and sample date.
5. Alternatively, to shorten the overall incubation period, two surface sampling media devices may be collected for each sample location and incubated concurrently.
   A. Both media devices could be TSA or one media device could be TSA and the other fungal media (e.g., malt extract agar [MEA] or Sabouraud dextrose agar [SDA]). Media must be supplemented with neutralizing additives (e.g., lecithin and polysorbate 80).
   B. Incubate each media device in a separate incubator. Incubate one media device at 30°–35° for no less than 48 h, and incubate the other media device at 20°–25° for no less than 5 days. If fungal media are used, incubate the fungal media device at 20°–25° for no less than 5 days.
   C. Count the total number of discrete colonies of microorganisms on each media device, and record these results as cfu per media device.
   D. Record the results of the sampling on an environmental sampling form based on sample type (i.e., surface), and include the sample location and sample date.

6.3.3 Surface sampling data evaluation and action levels: Evaluate cfu counts against the action levels in *Table 8*, and examine counts in relation to previous data to identify adverse results or trends. If two sampling media devices are collected at a single location, all recovered growth on each must be documented and action levels applied to each sampling media device separately. If levels measured during surface sampling exceed the levels in *Table 8* for the ISO classification levels of the area sampled, the cause must be investigated and corrective action must be taken. Data collected in response to corrective actions must be reviewed to confirm that the actions taken have been effective. The corrective action plan must be dependent on the cfu count and the microorganism recovered. Some examples of corrective action include process or facility improvements, personnel training, cleaning and disinfecting, or HEPA filter replacement and/or repair. The extent of the investigation should be consistent with the deviation and should include an evaluation of trends. The corrective action plan must be documented. If levels measured during surface sampling exceed the levels in *Table 8*, an attempt must be made to identify any microorganism recovered to the genus level (see ⟨1113⟩) with the assistance of a microbiologist.

Table 8. Action Levels for Surface Sampling

ISO Class	Surface Sampling Action Levels (cfu/media device)
5	>3
7	>5
8	>50

7. CLEANING, DISINFECTING, AND APPLYING SPORICIDAL DISINFECTANTS AND STERILE 70% IPA

Surfaces in classified areas used to prepare Category 1, Category 2, and Category 3 CSPs must be:

- Cleaned
- Disinfected

- Sporicidal disinfectants applied

according to the frequencies described in *Table 10* for each CSP category.

Additionally, in a PEC, sterile 70% IPA must be applied after cleaning and disinfecting, or after the application of a one-step disinfectant cleaner or sporicidal disinfectant, to remove any residue. Sterile 70% IPA must also be applied immediately before initiating compounding. During the compounding process sterile 70% IPA must be applied to the horizontal work surface, including any removable work trays, of the PEC at least every 30 min if the compounding process takes 30 min or less. If the compounding process takes more than 30 min, compounding must not be disrupted, and the work surface of the PEC must be disinfected immediately after compounding.

These activities are important because surfaces in classified areas and SCAs are a potential source of microbial contamination of CSPs.

The process of cleaning involves removing organic and inorganic materials from surfaces, usually with a manual or mechanical process and a cleaning agent. The process of disinfecting involves destruction of microorganisms, usually with a chemical agent. The process of applying a sporicidal disinfectant involves the destruction of bacterial and fungal spores. See *Table 9* for a summary of the purposes of the cleaning, disinfectant, and sporicidal disinfectants.

Table 9. Purpose of Cleaning, Disinfecting, and Sporicidal Disinfectants

Type of Agent	Purpose
Cleaning	An agent, usually containing a surfactant, used for the removal of substances (e.g., dirt, debris, microbes, and residual drugs or chemicals) from surfaces.
Disinfectant	A chemical or physical agent used on inanimate surfaces and objects to destroy fungi, viruses, and bacteria.
Sporicidal	A chemical or physical agent that destroys bacterial and fungal spores when used at a sufficient concentration for a specified contact time. It is expected to kill all vegetative microorganisms.

Surfaces must be cleaned prior to being disinfected with an EPA-registered disinfectant (or equivalent for entities outside the US) unless an EPA-registered (or equivalent for entities outside the US) one-step disinfectant cleaner is used to accomplish both the cleaning and disinfection in one step. A sporicidal disinfectant must also be applied. Some EPA-registered (or equivalent) one-step disinfectant cleaners may have sporicidal properties. Cleaning and disinfecting surfaces and applying a sporicidal disinfectant must occur at the minimum frequencies specified in *Table 10*.

All cleaning and disinfecting activities must be performed by trained and appropriately garbed personnel using facility-approved agents and procedures, which must be described in written SOPs. Personnel must be trained if there are any changes in the cleaning and disinfecting procedures. Cleaning must be performed in the direction of clean to dirty areas. The same floor mop may be used in both the buffer and anteroom, but only in that order. Mops used in areas where HDs are compounded must be dedicated for use only in those areas.

The frequency, method(s), and location(s) of cleaning, disinfecting, and applying sporicidal disinfectants must be established in written SOPs, in accordance with the manufacturer's instructions and must be followed by all cleaning personnel. The manufacturer's directions or published data for the minimum contact time must be followed for each of the cleaning, disinfecting, and sporicidal disinfectants used. When sterile 70% IPA is used, it must be allowed to dry. All cleaning, disinfecting, and application of sporicidal disinfectants must be documented according to the facility's SOPs.

Table 10. Minimum Frequency for Cleaning and Disinfecting Surfaces and Applying Sporicidal Disinfectants in Classified Areas and in the SCA[a]

Site	Cleaning	Disinfecting[b]	Applying Sporicidal Disinfectant
PEC(s) and equipment inside the PEC(s)	• Equipment and all interior surfaces of the PEC daily on days when compounding occurs and when surface contamination is known or suspected	• Equipment and all interior surfaces of the PEC daily on days when compounding occurs and when surface contamination is known or suspected	• Monthly for entities compounding Category 1 and/or Category 2 CSPs • Weekly for entities compounding Category 3 CSPs
Removable work tray of the PEC, when applicable	• Work surface of the tray daily on days when compounding occurs • All surfaces and the area underneath the work tray monthly	• Work surface of the tray on days when compounding occurs • All surfaces and the area underneath the work tray monthly	• Work surfaces of the tray monthly • All surfaces and the area underneath the work tray monthly
Pass-through chambers	• Daily on days when compounding occurs	• Daily on days when compounding occurs	• Monthly for entities compounding Category 1 and/or Category 2 CSPs • Weekly for entities compounding Category 3 CSPs
Work surface(s) outside the PEC	• Daily on days when compounding occurs	• Daily on days when compounding occurs	
Floor(s)	• Daily on days when compounding occurs	• Daily on days when compounding occurs	
Wall(s), door(s), and door frame(s)	• Monthly	• Monthly	• Monthly
Ceiling(s)[c]			
Storage shelving and bin(s)			
Equipment outside the PEC(s)			

[a] Cleaning of sinks is described in *4.4 Water Sources*.

[b] Many disinfectants registered by the EPA are one-step cleaning and disinfecting agents, which means that the disinfectant has been formulated to be effective in the presence of light-to-moderate soiling without a separate cleaning step.
[c] Ceilings of the SCA are required to be cleaned, disinfected, and applied with sporicidal disinfectant only when visibly soiled and when surface contamination is known or suspected.

7.1 Agents and Supplies for Cleaning, Disinfecting, and Applying Sporicidal Disinfectants

7.1.1 Agents: Cleaning and disinfecting agents must be selected and used with careful consideration of compatibilities, effectiveness, and user safety. Considerations when selecting and using disinfectants include their antimicrobial activity, inactivation by organic matter, residue, shelf life, preparation requirements of the agent, and suitability for surfaces being disinfected. After the disinfectant or sporicidal disinfectant is applied to the surface, the agent must be allowed to dwell for the minimum contact time specified by the manufacturer.

Cleaning, disinfecting and sporicidal agents used within the PEC must be sterile. When diluting concentrated cleaning and disinfecting agents for use in the PEC, sterile water must be used. In classified areas outside of the PEC, sterile cleaning and disinfecting agents should be used. When diluting concentrated cleaning and disinfecting agents for use outside of the PEC, sterile water should be used.

7.1.2 Supplies: All cleaning and disinfecting supplies (e.g., wipers, sponges, pads, and mop heads) with the exception of tool handles and holders must be low lint. In addition, cleaning and disinfecting supplies used in the PEC must be sterile with the exception of tool handles and holders, which must be cleaned and disinfected prior to use in a PEC.

Wipers, sponges, pads, and mop heads should be disposable. If disposable cleaning supplies are used, they must be discarded after each cleaning activity. Reusable cleaning tools must be made of cleanable materials (e.g., handles should not be made of wood or any other porous material) and must be cleaned and disinfected before and after each use. Reusable cleaning tools must be dedicated for use in the classified areas or SCA and must not be removed from these areas except for disposal. They must be discarded as determined based on the condition of the tools. Cleaning supplies used in the classified areas and SCAs must be disposed of in a manner that minimizes the potential for dispersing contaminants into the air (e.g., with minimal agitation, away from work surfaces).

Once opened, sterile cleaning and disinfecting agents and supplies (e.g., closed containers of sterile wipers) and sterile 70% IPA may be reused for a time period specified as by the manufacturer and/or described in the facility written SOPs.

7.2 Procedures for Cleaning, Disinfecting, and Applying Sporicidal Disinfectants and Sterile 70% IPA in the PEC

Clean, disinfect, and apply a sporicidal disinfectant to equipment and all interior surfaces in the PEC at the minimum frequencies specified in *Table 10*. See *Box 7* and *Box 8* for procedures for cleaning, disinfecting, and applying a sporicidal disinfectant in the PEC.

Box 7. Procedures for Cleaning and Disinfecting the PEC

- If necessary, remove visible particles, debris, or residue with an appropriate solution (e.g., *Sterile Water for Injection* or *Sterile Water for Irrigation*) using sterile, low-lint wipers.
- Using a sterile low-lint wiper, apply a sterile cleaning agent followed by a sterile EPA-registered disinfectant or apply a sterile EPA-registered (or equivalent for entities outside the US) one-step disinfectant cleaner to equipment and all interior surfaces of the PEC.
- Ensure the contact time specified by the manufacturer is achieved.
- Using a sterile low-lint wiper, apply sterile 70% IPA to equipment and all interior surfaces in the PEC.
- Allow the surface to dry completely before beginning compounding.

Box 8. Procedures for Applying a Sporicidal Disinfectant in the PEC

- If necessary, remove visible particles, debris, or residue with an appropriate solution (e.g., *Sterile Water for Injection* or *Sterile Water for Irrigation*) using sterile, low-lint wipers.
- After cleaning and disinfecting (see *Box 7*), apply the sterile sporicidal disinfectant using a sterile low-lint wiper to all surfaces and the area underneath the work tray; if the sporicidal disinfectant is a sterile EPA-registered (or equivalent for entities outside the US) one-step disinfectant sporicidal cleaner, separate cleaning and disinfecting steps are not required.
- Ensure the contact time specified by the manufacturer is achieved.
- Using a sterile low-lint wiper, apply sterile 70% IPA to all interior surfaces, including underneath the work tray.
- Allow the surface to dry completely before beginning compounding.

8. INTRODUCING ITEMS INTO THE SEC AND PEC

8.1 Introducing Items into the SEC

Before any item is introduced into the clean side of anteroom(s), placed into pass-through chamber(s), or brought into the SCA, providing that packaging integrity will not be compromised, it must be wiped with a sporicidal disinfectant, EPA-registered disinfectant, or sterile 70% IPA using low-lint wipers by personnel wearing gloves. If an EPA-registered disinfectant or sporicidal disinfectant is used, the agent must be allowed to dwell for the minimum contact time specified by the manufacturer. If sterile 70% IPA is used, it must be allowed to dry. The wiping procedure should not compromise the packaging integrity or render the product label unreadable.

8.2 Introducing Items into the PEC

Just before any item is introduced into the PEC, it must be wiped with sterile 70% IPA using sterile low-lint wipers and allowed to dry before use. When sterile items are received in sealed containers designed to keep them sterile until opening, the sterile items may be removed from the covering as the supplies are introduced into the ISO Class 5 PEC without the need to wipe the individual sterile supply items with sterile 70% IPA. The wiping procedure must not render the product label unreadable.

8.3 Use of Sterile 70% IPA on Critical Sites within the PEC

Critical sites (e.g., vial stoppers, ampule necks, and intravenous bag septums) must be wiped with sterile 70% IPA in the PEC to provide both chemical and mechanical actions to remove contaminants. The sterile 70% IPA must be allowed to dry before personnel enter or puncture stoppers and septums or break the necks of ampules.

9. EQUIPMENT, SUPPLIES, AND COMPONENTS

9.1 Equipment

PECs are described in *4.2.3 Types of PECs and placement*. Other equipment used in compounding CSPs (e.g., automated compounding devices [ACDs] and balances) should be of suitable composition such that the surfaces that contact components are not reactive or sorptive. Equipment that must be brought into classified areas must be wiped with a sporicidal disinfectant, EPA-registered disinfectant, or sterile 70% IPA using low-lint wipers.

Equipment must be placed in a manner that facilitates sterile compounding operations. The equipment must be capable of operating properly and within required performance parameters. Compounding personnel must follow established SOPs for the calibration, maintenance, cleaning, and use of the equipment based on the manufacturer's recommendations. Personnel must maintain records from equipment calibration, verification, and maintenance in accordance with the requirements in *20. Documentation*.

ACDs and other similar equipment are designed to assist in the compounding of preparations by delivering specific volumes of solution(s) automatically under computerized control.

Before using ACDs or other similar equipment, compounding personnel must conduct an accuracy assessment before the first use and again each day the equipment is used to compound CSPs. The precision of the equipment can be monitored based on an assessment of day-to-day variations in its accuracy measures. Compounding personnel must maintain a daily record of the accuracy measurements on the days the equipment is in use. Corrective actions must be implemented if accuracy measurements are outside the manufacturer's specification.

Weighing, measuring, or otherwise manipulating components that could generate airborne chemical particles (e.g., active pharmaceutical ingredients [APIs], added substances, conventionally manufactured products) must be evaluated to determine if these activities must be performed in a PEC or other closed system processing device (e.g., single use containment glove bag) to reduce the potential exposure to personnel or contamination of the facility or CSPs (See *4.2.6 Facilities preparing Category 2 or Category 3 CSPs from nonsterile starting component(s)*). The process evaluation must be carried out in accordance with the facility's SOPs and the assessment must be documented.

9.2 Supplies

Supplies (e.g., beakers, utensils, needles, syringes, filters, and tubing sets) should be of suitable composition such that the surfaces that contact components are not reactive or sorptive. Supplies in direct contact with the CSP must be sterile and depyrogenated.

9.3 Components

Compounding personnel must follow the facility's SOPs, which must address the selection, receipt, evaluation, handling, storage, and documentation of all CSP components, including all ingredients and container closures.

9.3.1 Component selection: Conventionally manufactured sterile products should be used when available and appropriate for the intended CSP.

When APIs are used:

- Must comply with the criteria in the *USP–NF* monograph, if one exists
- Must have a COA that includes the specifications (e.g., compendial requirements for quality) and that test results for the component show that the API meets expected quality
- In the United States, must be manufactured by an FDA-registered facility
- Outside of the United States, must comply with the laws and regulations of the applicable regulatory jurisdiction

For all components other than APIs:

- Must comply with the criteria in the *USP–NF* monograph, if one exists
- Must be accompanied by documentation (e.g., COA, labeling) that includes the specifications and test results and shows that the component meets the specifications
- In the US, should be manufactured by an FDA-registered facility
  - If a component cannot be obtained from an FDA-registered facility, the designated person(s) must select an acceptable and reliable source (see *Good Distribution Practices for Bulk Pharmaceutical Excipients* ⟨1197⟩). The compounding facility must establish the identity, strength, purity, and quality of the ingredients obtained from that supplier by reasonable means. Reasonable means may include but are not limited to visual inspections, evaluation of a COA supplied by the manufacturer, and/or verification by analytically testing a sample to determine conformance with the COA or other specifications.
- Outside of the US, must comply with the laws and regulations of the applicable regulatory jurisdiction

When CSPs are used as components, see *16. Use of CSPs as Components*. All APIs and other components used must be evaluated for suitability for use in sterile drug preparation. Components labeled with "not for pharmaceutical use", "not for injectable use", "not for human use" or an equivalent statement must not be used to compound for these purposes.

Each lot of commercially available sterile, depyrogenated containers and container closure systems must be accompanied by a COA or other documentation showing conformance with established specifications (i.e., sterility and depyrogenation requirements). If sterilization and depyrogenation of supplies or container closure systems are performed on site, the efficacy of each process must be established and documented (see *Sterilization of Compendial Articles* ⟨1229⟩).

9.3.2 Component receipt: Upon receipt of each lot of a component, the external packaging must be examined for evidence of deterioration and other aspects of unacceptable quality. Facility personnel must verify the labeling and condition of the component [e.g., whether the outer packaging is damaged and whether temperature-sensing indicators show that the component has been exposed to excessive temperature(s)].

Any component found to be of unacceptable quality must be promptly rejected, clearly labeled as rejected, and segregated from active stock to prevent use before appropriate disposal. Any other lots of that component from that vendor must be examined to determine whether other lots have the same defect.

The date of receipt by the compounding facility must be clearly marked on each API or added substance package that lacks a vendor expiration date. Packages of components (i.e., API and added substances) that lack a vendor's expiration date must be assigned a conservative expiration date, not to exceed 1 year after receipt by the compounding facility.

9.3.3 Component evaluation before use: Compounding personnel must ascertain before use that components for CSPs are of the correct identity, appropriate quality, within expiry date and have been stored under appropriate conditions. The following information should be used to make this determination: prescription or medication order, compounding record (CR), master formulation record (if used), vendor label(s), COA(s) of API(s) and other component(s), product labeling of any conventionally manufactured sterile products, labeling of CSP(s), and documentation of the compounding facility's storage conditions and practices.

All components must be reinspected before use. All packages must be reinspected to detect container breaks, looseness of the cap or closure, and deviation from the expected appearance, aroma, and/or texture of the contents that might have occurred during storage. Sterile container closures must be visually reinspected to ensure that they are free from defects that could compromise sterility and that they are otherwise suitable for their intended use.

Any component found to be of unacceptable quality must be promptly rejected, clearly labeled as rejected, and segregated from active stock to prevent use before appropriate disposal. Any other lots of that component from that vendor must be examined to determine whether other lots have the same defect.

9.3.4 Component handling and storage: All components must be handled and stored in a manner that prevents contamination, mix-ups, and deterioration.

Components must be stored in closed containers under temperature, humidity, and lighting conditions consistent with those indicated in official monographs or specified by the suppliers and/or manufacturers.

Personnel must monitor temperature in the area(s) where components are stored either manually at least once daily on days that the facility is open or by a continuous temperature recording device to determine whether the temperature remains within the appropriate range. The results of the temperature readings must be documented on a temperature log or stored in the continuous recording device and must be retrievable. All monitoring equipment must be calibrated or verified for accuracy as recommended by the manufacturer or every 12 months if not specified by the manufacturer.

10. STERILIZATION AND DEPYROGENATION

When selecting the sterilization method for CSPs prepared from one or more nonsterile starting components or using nonsterile supplies or devices, personnel must take into consideration the nature of the component(s), their physical and chemical properties, and the intended container closure system.

The sterilization method used must sterilize the CSP without degrading its physical and chemical stability (e.g., affecting its strength, purity, or quality) or the packaging integrity. (See also the ⟨1229⟩ series of chapters.)

The following must be considered when selecting an appropriate sterilization method:

- Terminal sterilization (e.g., steam, dry heat, or irradiation) is the preferred method unless the specific CSP or container closure system cannot tolerate terminal sterilization
- Steam sterilization is not an option if moisture, pressure, or the temperatures used would degrade the CSP or if there is insufficient moisture to sterilize the CSP within the final, sealed, container closure system
- Filtration may not be an option for some compounded preparations, for example preparations with suspended drug particles or emulsions with a significant droplet size.

CSPs that are terminally sterilized (e.g., steam, dry heat, or irradiation) must use a process intended to achieve a probability of a nonsterile unit (PNSU) of 10^{-6}. [NOTE—This is also called the sterility assurance level (SAL).] A PNSU of 10^{-6} is equivalent to a probability that 1 unit in a million is nonsterile. A PNSU value cannot be applied to CSPs that are aseptically filled into a sterile container following sterilization by filtration because sterilization by filtration is not terminal sterilization.

Injectable compounded preparations that contain nonsterile components or that come into contact with nonsterile devices (e.g., containers, tubing) during any phase of the compounding procedure must be sterilized within 6 h after completing the preparation to minimize the generation of bacterial endotoxins in CSPs.

A description of the terminal sterilization and depyrogenation process, including the temperature, pressure (if applicable), duration, permissible load conditions for each cycle, and the use of biological indicators and endotoxin challenge vials (ECVs) must be included in the facility's SOPs.

SOPs must include training and competency of personnel on all sterilization methods and equipment used by the facility. In addition, the SOPs must include a schedule and method for establishing and verifying the effectiveness of the terminal sterilization and depyrogenation methods selected, as well as the methods for maintaining and cleaning the sterilizing and depyrogenation equipment.

10.1 Depyrogenation

See *Dry Heat Depyrogenation* ⟨1228.1⟩. Dry heat depyrogenation must be used to render glassware, metal, and other thermostable containers and components pyrogen free. Depyrogenation processes typically operate at a range of temperatures, from approximately 170°–400°, depending on the exposure time (e.g., a cycle might hold the items at 250° for 30 min to achieve sterility and depyrogenation). The duration of the exposure period must include sufficient time for the items to reach the depyrogenation temperature. The items must remain at the depyrogenation temperature for the duration of the depyrogenation period.

The effectiveness of the dry heat depyrogenation cycle must be established initially and verified annually using ECVs to demonstrate that the cycle is capable of achieving a ≥3-log reduction in endotoxins (see *Bacterial Endotoxins Test* ⟨85⟩). The effectiveness of the depyrogenation cycle must be re-established if there are changes to the depyrogenation cycle described in SOPs (e.g., changes in load conditions, duration, or temperature). This verification must be documented.

Items that are not thermostable must be depyrogenated by multiple rinses with sterile, nonpyrogenic water (e.g., *Sterile Water for Injection* or *Sterile Water for Irrigation*) and then thoroughly drained or dried immediately before use in compounding See *Depyrogenation by Rinsing* ⟨1228.4⟩.

10.2 Sterilization by Filtration

See *Sterilizing Filtration of Liquids* ⟨1229.4⟩. Sterilizing filters must be sterile, depyrogenated, have a nominal pore size of 0.22 µm or smaller, and be appropriate for pharmaceutical use. Sterilizing filters with labeling that states "for laboratory use only" or a similar statement must not be used for compounding CSPs. Sterilizing filters must be certified by the manufacturer to retain at least 10^7 microorganisms of a strain of *Brevundimonas diminuta* per square centimeter of upstream filter surface area under conditions similar to those in which the CSPs will be filtered (i.e., pressure, flow rate, and volume filtered).

The designated person(s) must ensure—from available published information, from supplier documentation, or through direct challenge (e.g., filtering the CSP)—that the filters 1) are chemically and physically compatible with all ingredients in the CSP (e.g., water-miscible alcohols may damage filter integrity); 2) are chemically stable at the pressure and temperature conditions that will be used; and 3) have enough capacity to filter the required volumes. The filter dimensions and the CSP to be sterilized by filtration should permit the sterilization process to be completed without the need for replacement of the filter during the process. Filter units used to sterilize CSPs must be subjected to the manufacturers' recommended integrity testing, such as a post-use bubble point test. If multiple filters are required for the compounding process, each of the filters must pass a filter-integrity test.

When CSPs are known to contain excessive particulate matter, a prefiltration step must be performed using a filter of larger nominal pore size (e.g., 1.2 µm) or a separate filter of larger nominal pore size should be placed upstream of (i.e., prior to) the sterilizing filter to remove gross particulate contaminants before the CSP is passed through the sterilizing-grade filter. Excessive particulate matter requiring a prefiltration step could potentially be a signal of an inappropriate formulation, and therefore the formulation and the process should be assessed and modified if necessary. CSPs that were prepared using a filter that failed integrity tests must be discarded or, after investigating the cause of the failure and selection of an appropriate filter, refiltered for sterilization not more than one additional time.

10.3 Sterilization by Steam Heat

Temperatures used to achieve sterilization by steam heat are lower than those used to achieve depyrogenation. The process of thermal sterilization using saturated steam under pressure (i.e., autoclaving) is the preferred method for terminal sterilization of aqueous CSPs in their final, sealed container closure system (see *Steam Sterilization by Direct Contact* ⟨1229.1⟩). Steam sterilization is not an option if moisture, pressure, or the temperatures used would degrade the CSP.

To achieve sterility when steam sterilization is used, all materials must be directly exposed to steam under adequate pressure for the length of time necessary, as determined by use of appropriate biological indicators, to render the items sterile (e.g., 20–60 min at 121° saturated steam under a pressure of 15 psi, depending on the volume or size of the CSP being sterilized). The duration of the exposure period must include sufficient time for the entire contents of the CSP and other items to reach the sterilizing temperature. The CSP and other items must remain at the sterilizing temperature for the duration of the sterilization period.

CSPs must be placed in the autoclave to allow steam to reach the CSPs without entrapment of air. Flat, stainless-steel trays with low sides or ventilated bottoms will permit steam contact. When preparing items that must be wrapped for steam sterilization, wrap them in low-lint protective fabric or paper or seal in envelopes that will permit steam penetration and are designed to minimize the risk of post-sterilization microbial contamination. For CSPs, immediately before filling containers that will be steam sterilized, solutions must be passed through a filter with a nominal pore size of not larger than 1.2 µm for removal of particulate matter.

Sealed containers must be able to generate steam internally. Stoppered and crimped empty vials must contain a small amount of sterile water to generate steam.

The effectiveness of steam sterilization must be verified and documented with each sterilization run or load by using appropriate biological indicators, such as spores of *Geobacillus stearothermophilus* (ATCC 12980, ATCC 7953, or equivalent; see *Biological Indicators for Sterilization* ⟨1229.5⟩), and other confirmation methods such as physicochemical indicators (see *Physicochemical Integrators and Indicators for Sterilization* ⟨1229.9⟩).

The steam supplied must be generated using water per the manufacturer's recommendation. A calibrated data recorder or chart must be used to monitor each cycle and to examine for cycle irregularities (e.g., deviations in temperature or pressure). The date, run, and load numbers of the steam sterilizer used to sterilize a CSP must be documented in the CR.

10.4 Sterilization by Dry Heat

Dry heat may be used for those items that cannot be sterilized by steam or other means when the moisture would damage the material or the wrapping material is impermeable (see *Dry Heat Sterilization* ⟨1229.8⟩). Sterilization by dry heat requires higher temperatures and longer exposure times than sterilization by steam. The duration of the exposure period must include sufficient time for the entire contents of CSPs and other items to reach the sterilizing temperature. The CSP and other items must remain at the sterilizing temperature for the duration of the sterilization period. Immediately before filling ampules and vials that will be sterilized by dry heat, CSP solutions must be passed through a filter with a nominal pore size of not larger than 1.2 µm for removal of particulate matter.

Dry heat sterilization is usually performed in an oven designed for sterilization at 160° or higher. If lower temperatures are used, they must be shown to achieve effective sterilization (see ⟨1229.8⟩*, Validation of Dry Heat Sterilization, Biological Indicators*).

Heated air must be evenly distributed throughout the chamber, which is typically accomplished by an air blower. The calibrated oven must be equipped with temperature controls and a timer. During sterilization, sufficient space must be left between materials to allow for circulation of the hot air. A calibrated data recorder or chart must be used to monitor each cycle and the data must be reviewed to identify cycle irregularities (e.g., deviations in temperature or exposure time).

The effectiveness of the dry heat sterilization method must be verified and documented with each sterilization run or load using appropriate biological indicators such as spores of *Bacillus atrophaeus* (ATCC 9372; see ⟨1229.5⟩) and other confirmation methods (e.g., temperature-sensing devices). The date, run, and load numbers of the dry heat oven used to sterilize a CSP must be documented in the CR.

11. MASTER FORMULATION AND COMPOUNDING RECORDS

11.1 Creating Master Formulation Records

A master formulation record (MFR) is a detailed record of procedures that describes how the CSP is to be prepared. An MFR must be created for all CSPs prepared from nonsterile ingredient(s) or CSPs prepared for more than one patient. Any changes or alterations to the MFR must be approved and documented according to the facility's SOPs. *Box 9* lists the information that must be included in an MFR.

Box 9. Master Formulation Records

An MFR must include at least the following information:

- Name, strength or activity, and dosage form of the CSP
- Identities and amounts of all ingredients; if applicable, relevant characteristics of components (e.g., particle size, salt form, purity grade, solubility)
- Type and size of container closure system(s)
- Complete instructions for preparing the CSP, including equipment, supplies, a description of the compounding steps, and any special precautions
- Physical description of the final CSP
- BUD and storage requirements
- Reference source to support the stability of the CSP
- Quality control (QC) procedures (e.g., pH testing, filter integrity testing)
- Other information as needed to describe the compounding process and ensure repeatability (e.g., adjusting pH and tonicity; sterilization method, such as steam, dry heat, irradiation, or filter)

11.2 Creating Compounding Records

A CR documents the compounding of each CSP. A CR must be created for all Category 1, Category 2, and Category 3 CSPs. A CR must also be created for immediate-use CSPs prepared for more than one patient. The CR must be created to document the compounding process. A prescription or medication order or label may serve as the CR. If an ACD, workflow management system, or other similar equipment is used, the required information in the CR may be stored electronically as long as it is retrievable and contains the required information (see *Box 10*). An MFR can serve as the basis for preparing the CR. For example, a copy of the MFR can be made that contains spaces for recording the information needed to complete the CR. *Box 10* lists the information that must be included in a CR.

Box 10. Compounding Records

CRs must include at least the following information:

- Name, strength or activity, and dosage form of the CSP
- Date and time of preparation of the CSP
- Assigned internal identification number (e.g., prescription, order, or lot number)
- A method to identify the individuals involved in the compounding process and individuals verifying the final CSP
- Name of each component
- Vendor, lot number, and expiration date for each component for CSPs prepared for more than one patient and for CSPs prepared from nonsterile ingredient(s)
- Weight or volume of each component
- Strength or activity of each component
- Total quantity compounded
- Final yield (e.g., quantity, containers, number of units)
- Assigned BUD and storage requirements
- Results of QC procedures (e.g., visual inspection, filter integrity testing, pH testing)

If applicable, the CR must also include:

- MFR reference for the CSP
- Calculations made to determine and verify quantities and/or concentrations of components

12. RELEASE INSPECTIONS AND TESTING

All release testing procedures (e.g., visual inspections and testing) must be included in the facility's documentation (see *11. Master Formulation and Compounding Records* and *17. SOPs*). Any out-of-specification results must be investigated, and a corrective action plan must be implemented and documented as part of the quality assurance (QA) and QC program (see *18. Quality Assurance and Quality Control*).

12.1 Visual Inspection

At the completion of compounding, before release and dispensing, the CSP must be visually inspected to determine whether the physical appearance of the CSP is as expected (e.g., free of inappropriate visible particulates or other foreign matter, discoloration, or other defects). The CSP label must be visually inspected to confirm that the CSP and its labeling match the prescription or medication order. The inspection also must include a visual inspection of container closure integrity (e.g., checking for leakage, cracks in the container, or improper seals). Any CSP found to be of unacceptable quality (e.g., observed defects) must be promptly rejected, clearly labeled as rejected, and segregated from active stock to prevent use before appropriate disposal.

When a CSP will not be released or dispensed on the day of preparation, a visual inspection must be conducted immediately before it is released or dispensed to make sure that the CSP does not exhibit any defects such as precipitation, cloudiness, or leakage, which could develop during storage. Any CSP found to be of unacceptable quality (e.g., observed defects) must be promptly rejected, clearly labeled as rejected, and segregated from active stock to prevent use before appropriate disposal. Defects that indicate sterility or stability problems must be investigated to determine the cause according to the facility's SOPs (see *18. Quality Assurance and Quality Control*).

12.2 Sterility Testing

Sterility testing is not required for Category 1 CSPs (see *Table 12*). For Category 2 CSPs assigned a BUD that requires sterility testing (see *Table 13*) and all Category 3 CSPs, the testing must be performed according to ⟨71⟩ or a validated alternative method (see ⟨1223⟩) that is noninferior to ⟨71⟩ testing.

If sterility testing is performed, the minimum quantity of each container to be tested for each media is specified in ⟨71⟩, *Table 2*, and the number of containers required to be tested in relation to the batch size is specified in ⟨71⟩, *Table 3*, except as described below. The maximum batch size for all CSPs requiring sterility testing must be limited to 250 final yield units.

If the number of CSPs to be compounded in a single batch is less than the number of CSPs needed for testing as specified in ⟨71⟩, *Table 3*, additional units must be compounded to perform sterility testing as follows:

- If 1–39 CSPs are compounded in a single batch, the sterility testing must be performed on a number of units equal to 10% of the number of CSPs prepared, rounded up to the next whole number. For example:
  - If 1 CSP is compounded, 10% of 1 rounded up to the next whole number would indicate that 1 additional CSP must be prepared for sterility testing
  - If 39 CSPs are compounded, 10% of 39 rounded up to the next whole number would indicate that 4 additional CSPs must be prepared for sterility testing
- If more than 40 CSPs are prepared in a single batch, the sample sizes specified in ⟨71⟩, *Table 3* must be used.

If sterility testing is performed according to ⟨71⟩, the *Method Suitability Test* from that chapter must be performed to ensure that contamination can be recovered. If performing sterility testing according to ⟨71⟩, the *Membrane Filtration* method from that chapter is the method of choice when the CSP formulation permits. The preferred alternative is the ⟨71⟩, *Test for Sterility of the Product to Be Examined, Direct Inoculation of the Culture Medium* method. If an alternative method is used for sterility testing, the method must be validated (see ⟨1223⟩) and demonstrated to be suitable for that CSP formulation.

Sterility tests resulting in failures must prompt an investigation into the possible causes and must include identification of the microorganism, as well as an evaluation of the sterility testing procedure, compounding facility, process, and/or personnel that may have contributed to the failure. The source(s) of the contamination, if identified, must be corrected, and the facility must determine whether the conditions causing the sterility failure affect other CSPs. The investigation and resulting corrective actions must be documented.

12.3 Bacterial Endotoxins Testing

Category 1 injectable CSPs do not require testing for bacterial endotoxins. Category 2 injectable CSPs compounded from one or more nonsterile component(s) and assigned a BUD that requires sterility testing (see *Table 13*) and Category 3 injectable CSPs compounded from one or more nonsterile component(s) must be tested to ensure that they do not contain excessive bacterial endotoxins (see ⟨85⟩). Category 2 injectable CSPs compounded from one or more nonsterile component(s) and assigned a BUD that does not require sterility testing should be tested for bacterial endotoxins. In the absence of a bacterial endotoxin limit in an official *USP–NF* monograph or other CSP formula source, the CSP must not exceed the endotoxin limit calculated as described in ⟨85⟩ for the appropriate route of administration for humans. CSPs for nonhuman species must not exceed the endotoxin limit calculated as described in ⟨85⟩ based on the largest recommended dose and weight (or average weight for more than a single animal) of the target animal species unless a different limit is scientifically supported. CSPs administered epidurally should have the same endotoxin limit as that of intrathecally administered CSPs. See also *Guidelines on the Endotoxins Test* ⟨1085⟩.

13. LABELING

Category 1, Category 2, and Category 3 CSPs must be labeled with appropriate, legible identifying information to prevent errors during storage, dispensing, and use. The term *labeling* designates all labels and other written, printed, or graphic matter on the immediate container or on or inside any package or wrapper in which it is enclosed, except any outer shipping container. The term *label* designates that part of the labeling that is on the immediate container. See *Labeling* ⟨7⟩.

All labeling must be in compliance with laws and regulations of the applicable regulatory jurisdiction.

The label on each immediate container of the CSP must, at a minimum, display prominently and legibly the following information:

- Assigned internal identification number (e.g., barcode, prescription, order, or lot number)
- Active ingredient(s) and their amount(s), activity(ies), or concentration(s)
- Storage conditions if other than controlled room temperature
- BUD
- Dosage form
- Total amount or volume if it is not obvious from the container
- If it is a single-dose container, a statement stating such when space permits
- If it is a multiple-dose container, a statement stating such

The labeling on the CSP must display the following information, as applicable:

- Route(s) of administration
- Special handling instructions
- Warning statements
- Compounding facility name and contact information if the CSP is to be sent outside of the facility or healthcare system in which it was compounded

The labeling on the CSP should indicate that the preparation is compounded.

Labeling procedures must be followed as described in the facility's SOPs to prevent labeling errors and CSP mix-ups. The label of the CSP must be verified to ensure that it conforms with the

1. Prescription or medication order;

2. MFR, if required (see *11.1 Creating Master Formulation Records*); and
3. CR, if required (see *11.2 Creating Compounding Records*)

14. ESTABLISHING BEYOND-USE DATES

14.1 Terminology

Each CSP label must state the date, or the hour and date, beyond which the preparation must not be used and must be discarded (i.e., the BUD). The BUD is determined from the date and time that preparation of the CSP is initiated. The BUD is not intended to limit the time during which the CSP is administered (e.g., infused).

BUDs and expiration dates are not the same. An expiration date identifies the time during which a conventionally manufactured product, API, or added substance can be expected to meet the requirements of a *USP–NF* monograph, if one exists, or maintain expected quality provided it is kept under the specified storage conditions. The expiration date limits the time during which a conventionally manufactured product, API, or added substance may be dispensed or used (see ⟨*7*⟩*, Labels and Labeling for Products in Other Categories, Expiration Date and Beyond-Use Date*). Expiration dates are assigned by manufacturers based on analytical and performance testing of the sterility, chemical and physical stability, and packaging integrity of the product. Expiration dates are specific to a particular formulation in its container and at stated exposure conditions of illumination and temperature. See *Table 11* for a summary of terms.

Table 11. Summary of Terms

Term	Definition	Applicability
BUD	Either the date, or hour and date, after which a CSP must not be used. The BUD is determined from the date and time that preparation of the CSP is initiated	Applies to all CSPs
Expiration date	The time during which a product can be expected to meet the requirements of the *USP–NF* monograph, if one exists, or maintain expected quality provided it is kept under the specified storage conditions.	Applies to all conventionally manufactured products, APIs, and added substances

14.2 Parameters to Consider in Establishing a BUD

BUDs for CSPs should be established conservatively to ensure that the drug maintains its required characteristics (i.e., stability and sterility) until its BUD.

When establishing a BUD for a CSP, compounders must consider parameters that may affect quality, including but not limited to:

- Chemical and physical stability properties of the drug and/or its formulation
- Materials of composition of the container closure system and compatibility of the container closure system with the final preparation (e.g., leachables, interactions, adsorption, and storage conditions)

The BUDs for CSPs are based primarily on factors that affect the achievement and maintenance of sterility, which include but are not limited to the following:

- Conditions of the environment in which the CSP is prepared
- Aseptic processing and sterilization method
- Starting components (e.g., sterile or nonsterile ingredients)
- Whether or not sterility testing is performed
- Storage conditions (e.g., packaging and temperature)

14.2.1 Terminal sterilization methods and aseptic processing: A CSP may be prepared by the following methods (see *10. Sterilization and Depyrogenation*):

- Terminal sterilization, which includes compounding with sterile and/or nonsterile starting ingredient(s) and subsequent sterilization with a process intended to achieve a PNSU of 10^{-6} (e.g., steam, dry heat, irradiation).
- Aseptic processing, which includes 1) compounding with only sterile starting ingredient(s) or 2) compounding with nonsterile ingredient(s) followed by sterilization by filtration. [NOTE—Sterilization by filtration is not a form of terminal sterilization.]

Terminal sterilization is the preferred method of sterilization, unless the specific CSP or container closure system cannot tolerate terminal sterilization. *Table 13* allows for longer BUDs for terminally sterilized CSPs than for aseptically processed CSPs because terminal sterilization using a verified method provides reasonable assurance that a CSP will be sterile.

14.2.2 Starting components: The use of one or more nonsterile starting component(s) is a risk factor to be considered when preparing a CSP. A longer BUD is permitted for CSPs that are aseptically processed from conventionally manufactured sterile starting component(s) than from one or more nonsterile starting component(s).

14.2.3 Sterility testing: Sterility testing (see *12.2 Sterility Testing*) of a CSP can provide additional assurance of the absence of contamination, although passing a sterility test does not guarantee that all units of a batch of CSPs are sterile because contamination may not be uniformly distributed throughout the batch. A longer BUD is permitted if sterility testing results are within acceptable limits. The maximum batch size for all CSPs requiring sterility testing must be limited to 250 final yield units.

14.2.4 Storage conditions: Storage in colder conditions (i.e., in a refrigerator or freezer [see *Packaging and Storage Requirements* ⟨659⟩]) has been shown to slow the growth of most microorganisms. However, the chemical and physical stability of the CSP and its components must be considered when storing in colder conditions (e.g., some formulations may precipitate when stored in a refrigerator or freezer). A longer BUD is permitted in *Table 12* and *Table 13* for CSPs stored in colder conditions than for CSPs stored at controlled room temperature.

If the CSP will be stored in a frozen state, the container closure system must be able to withstand the physical stress (i.e., without breaking or cracking) during storage in a freezer. The CSP must be thawed in appropriate conditions to avoid compromising the physical and chemical stability of the preparation and its components (e.g., do not heat in a microwave). Once the CSP is thawed, the CSP must not be refrozen.

CSPs may be stored under different storage conditions before they are used (e.g., CSPs may first be frozen, then thawed in the refrigerator, and finally kept at controlled room temperature before administration). The storage time of a CSP must not exceed the original BUD placed on the CSP for its labeled storage condition, and BUDs must not be additive. For example, an aseptically processed CSP prepared from one or more nonsterile starting component(s) cannot be stored for 45 days in a freezer, then 4 days refrigerated, and then 24 h at controlled room temperature for a total of 50 days. Once a CSP has been stored under a condition that would require a shorter BUD (e.g., controlled room temperature), the CSP must be used within the time frame for that storage condition (in the previous example, 24 h).

14.3 Establishing a BUD for a CSP

BUDs for CSPs must be established in accordance with *Table 12* for Category 1 CSPs, *Table 13* for Category 2 CSPs and *Table 14* for Category 3 CSPs. One day is equivalent to 24 h.

The BUD limits in these tables are based on the risk of microbial contamination or not achieving and maintaining sterility despite implementation of the requirements in this chapter. The CSP formulation must remain chemically and physically stable, and its packaging must maintain its integrity for the duration of the BUD.

A shorter BUD must be assigned when the stability of the CSP or its components is less than the hours or days stated in the applicable table below. Additionally:

- The BUD must not exceed the shortest remaining expiration date of any of the commercially available starting components.
- For CSPs prepared from one or more compounded components, the BUD should generally not exceed the shortest BUD of any of the individual compounded components. However, there may be acceptable instances when the BUD of the final CSP exceeds the BUD assigned to compounded components (e.g., pH-altering solutions). If the assigned BUD of the final CSP exceeds the BUD of the compounded components, the physical, chemical, and microbiological quality of the final CSP must not be negatively impacted.

Table 12 establishes the longest permitted BUDs for Category 1 CSPs. Category 1 CSPs may be prepared in an SCA or cleanroom suite (see *4.2 Facility Design and Environmental Controls*).

Table 12. BUD Limits for Category 1 CSPs[a]

Storage Conditions	
Controlled Room Temperature (20°–25°)	**Refrigerator (2°–8°)**
≤12 h	≤24 h

[a] A shorter BUD must be assigned when the physical and chemical stability of the CSP is less than the BUD limit stated in the table.

Table 13 establishes the longest permitted BUDs for Category 2 CSPs. Category 2 CSPs must be prepared in a cleanroom suite (see *4.2 Facility Design and Environmental Controls*).

Table 13. BUD Limits for Category 2 CSPs[a]

Preparation Characteristics		Storage Conditions		
Compounding Method	**Sterility Testing Performed and Passed**	**Controlled Room Temperature (20°–25°)**	**Refrigerator (2°–8°)**	**Freezer (–25° to –10°)**
Aseptically processed CSPs	No	Prepared from one or more nonsterile starting component(s): 1 day	Prepared from one or more nonsterile starting component(s): 4 days	Prepared from one or more nonsterile starting component(s): 45 days
		Prepared from only sterile starting components: 4 days	Prepared from only sterile starting components: 10 days	Prepared from only sterile starting components: 45 days
	Yes	30 days	45 days	60 days
Terminally sterilized CSPs	No	14 days	28 days	45 days
	Yes	45 days	60 days	90 days

[a] A shorter BUD must be assigned when the physical and chemical stability of the CSP is less than the BUD limit stated in the table.

14.4 Additional Requirements for Category 3 CSPs

14.4.1 Assigning Category 3 BUDs: Increasing the storage time of a CSP introduces additional risk for chemical degradation, physical incompatibilities, the compromising of the container closure system, and microbial proliferation. To address these risks and maintain a higher state of environmental control, additional requirements must be met when assigning BUDs for Category 3 CSPs in accordance with *Table 14*. Category 3 CSPs must not be assigned a BUD longer than the limits in *Table 14*.

14.4.2 Facility and Personnel Requirements for Category 3 CSPs: In addition to the requirements in this section, other facility and personnel requirements related to compounding Category 3 CSPs are addressed throughout the chapter.

- Category 3 personnel competency requirements apply to personnel who participate in or oversee the compounding of Category 3 CSPs (see *2.2 Demonstrating Competency in Garbing and Hand Hygiene* and *2.3 Competency Testing in Aseptic Manipulation*).
- Category 3 garbing requirements apply to all personnel entering the buffer room where Category 3 CSPs are compounded and apply at all times regardless of whether Category 3 CSPs are being compounded on a given day (see *3.3 Garbing Requirements*).
- Increased environmental monitoring requirements apply to all classified areas where Category 3 CSPs are compounded and apply at all times regardless of whether Category 3 CSPs are being compounded on a given day (see *6.2 Monitoring Air Quality for Viable Airborne Particles* and *6.3 Monitoring Surfaces for Viable Particles*).
- The frequency of application of sporicidal disinfectants applies to all classified areas where Category 3 CSPs are compounded and applies at all times regardless of whether Category 3 CSPs are being compounded on a given day (see *Table 10*).

14.4.3 Stability Requirements for Category 3 CSPs: The BUD assigned to a Category 3 CSP must be supported by stability data obtained using a stability-indicating analytical method that is able to distinguish the active ingredient from its degradants and impurities (e.g., by forced degradation studies) and quantify the amount of the active ingredient.

- The Category 3 CSP must be prepared according to the exact formulation (API and other ingredients of identical grade and procedures) from which the stability data are derived.
- The Category 3 CSP must be packaged and stored in a container closure of the same materials of composition as that used in the study.
- The analytical method must be validated based on characteristics such as those described in ⟨1225⟩.
- The compounding facility must have documentation of the stability study, including a description of the methodology (e.g., number of samples taken, storage conditions), validation of the method, the stability-indicating analytical method, and all of the results of the study.

If the Category 3 CSP is an injection (*Particulate Matter in Injections* ⟨788⟩) or if it is an ophthalmic solution (*Particulate Matter in Ophthalmic Solutions* ⟨789⟩), particulate-matter testing is conducted once per formulation with acceptable results.

Once for each formulation and for each container closure system in which it will be packaged, the container closure system used is evaluated for and conforms to container closure integrity to the end of the BUD (see *Package Integrity Evaluation—Sterile Products* ⟨1207⟩).

14.4.4 Release testing for Category 3 CSPs

- Each time the Category 3 CSP is prepared, it is sterility tested and meets the requirements of ⟨71⟩ or a validated alternative method (see *Table 14*) that is noninferior to ⟨71⟩ testing.
- Each time the Category 3 CSP is prepared, it is tested for endotoxins for acceptable results, if endotoxin testing is required under *12.3 Bacterial Endotoxins Testing*.

Table 14 establishes the longest permitted BUDs for Category 3 CSPs. If all of the conditions described for Category 3 CSPs in this chapter are not met, the applicable BUD in *Table 13* must not be exceeded.

Table 14: BUD Limits for Category 3 CSPs[a]

Preparation Characteristics	Storage Conditions		
Compounding Method	Controlled Room Temperature (20°–25°)	Refrigerator (2°–8°)	Freezer (–25° to –10°)
Aseptically processed, sterility tested, and passing all applicable tests for Category 3 CSPs	60 days	90 days	120 days
Terminally sterilized, sterility tested, and passing all applicable tests for Category 3 CSPs	90 days	120 days	180 days

[a] A shorter BUD must be assigned when the physical and chemical stability of the CSP is less than the BUD limit stated in the table.

14.5 Multiple-Dose CSPs

A compounded multiple-dose container is designed to contain more than one dose, intended to be entered or penetrated multiple times, and usually contains a preservative. A preservative is intended to inhibit the growth of microorganisms and minimize the risk of contamination. The use of preservatives must be appropriate for the CSP formulation and the route of administration. For example, the preservative must not be inactivated by any ingredients in the CSP, and some preservatives are not always appropriate for the patient (e.g., neonates) or route of administration (e.g., intrathecal or ophthalmic injection). The use of preservatives, however, must not be considered a substitute for aseptic technique.

A multiple-dose CSP must be prepared as a Category 2 or Category 3 CSP. An aqueous multiple-dose CSP must additionally pass antimicrobial effectiveness testing in accordance with *Antimicrobial Effectiveness Testing* ⟨51⟩. The compounder may rely on antimicrobial effectiveness testing 1) conducted (or contracted for) once for each formulation in the particular container closure system in which it will be packaged or 2) results from an FDA-registered facility or published in peer-reviewed literature sources, provided that the CSP formulation (including any preservative) and container closure system are exactly the same as those tested, unless a bracketing study is performed. Antimicrobial effectiveness testing may be performed on a low concentration and a high concentration of the active ingredient in the formulation to establish preservative effectiveness across various strengths of the same formulation (e.g., bracketing). The concentration of all other ingredients (including preservatives) must be the same throughout the bracketing study.

After a multiple-dose CSP container is initially entered or punctured, the multiple-dose container must not be used for longer than the assigned BUD or 28 days if supported by antimicrobial effectiveness testing results (see ⟨51⟩) on the CSP, whichever is shorter.

The container closure system used to package the multiple-dose CSP must be evaluated for and conform to container closure integrity (see ⟨1207⟩). The container closure integrity test needs to be conducted only once on each formulation and on fill volume in the particular container closure system in which the multiple-dose CSP will be packaged.

Multiple-dose, nonpreserved, aqueous topical, and topical ophthalmic, CSPs: The beyond-use date of a multiple-dose, aqueous, nonpreserved CSP intended for topical, including topical ophthalmic, administration may be assigned in accordance with *14.5 Multiple-Dose CSPs*. However, unpreserved aqueous, topical, including topical ophthalmic, formulations, are at high risk of microbial proliferation if contaminated during preparation or use. To minimize the risk of patient harm, the requirement for passing antimicrobial effectiveness testing in accordance with ⟨51⟩ is not required only if the preparation is:

- Prepared as a Category 2 or Category 3 CSP
- For use by a single patient
- Labeled (in the label or labeling) to indicate that once opened, it must be discarded after 24 h when stored at controlled room temperature and/or that once opened, it must be discarded after 72 h when stored under refrigeration

15. USE OF CONVENTIONALLY MANUFACTURED PRODUCTS AS COMPONENTS

This section addresses the time within which an entered or punctured conventionally manufactured product must be used.

15.1 Use of Conventionally Manufactured Single-Dose Containers

A conventionally manufactured single-dose container is a container closure system that holds a sterile product for parenteral administration (injection or infusion) that is not required to meet the antimicrobial effectiveness testing requirements. If a single-dose vial is entered or punctured only in an ISO Class 5 or cleaner air, it may be used up to 12 h after initial entry or puncture as long as the labeled storage requirements during that 12-h period are maintained. Opened single-dose ampules must not be stored for any time period.

15.2 Use of Conventionally Manufactured Multiple-Dose Containers

A conventionally manufactured product in a multiple-dose container is intended to contain more than one dose of a drug product (see ⟨659⟩*, General Definitions, Injection Packaging Systems*). Once initially entering or puncturing the multiple-dose container, the multiple-dose container must not be used for more than 28 days (see ⟨51⟩) unless otherwise specified by the manufacturer on the labeling.

15.3 Use of Conventionally Manufactured Pharmacy Bulk Packages

A conventionally manufactured pharmacy bulk package is a container of a sterile product for parenteral use that contains many single doses. The contents are intended for use in a pharmacy admixture program and are restricted to the sterile preparation of admixtures for infusion or, through a sterile transfer device, for the filling of empty sterile containers. The pharmacy bulk package must be used according to the manufacturer's labeling (see ⟨659⟩*, General Definitions, Injection Packaging Systems*). The pharmacy bulk package must be entered or punctured only in an ISO Class 5 PEC.

16. USE OF CSPs AS COMPONENTS

This section addresses the use of CSPs (e.g., multiple-dose CSPs, single-dose CSPs, and compounded stock solutions) as components to prepare final CSPs.

When a CSP is used as a component, care must be taken to minimize the risk of contamination of both the starting component CSP and the final CSP(s).

- *Component CSP*: The component CSP must be assigned a BUD consistent with *14. Establishing Beyond-Use Dates* and must be stored under conditions for its assigned BUD when not in use.
- *Final CSP*: The final CSP must be assigned a BUD consistent with *14. Establishing Beyond-Use Dates*.

16.1 Use of Compounded Multiple-Dose CSPs

A multiple-dose CSP is designed to contain more than one dose of sterile preparation, intended to be entered or punctured multiple times, and usually contains a preservative. Multiple-dose CSPs are required to meet the criteria for antimicrobial effectiveness testing (see ⟨51⟩) and the requirements in *14.5 Multiple-Dose CSPs*. Multiple-dose CSPs must be stored under the conditions upon which its BUD is based (e.g., refrigerator or controlled room temperature). After a multiple-dose CSP is initially entered or punctured, the multiple-dose CSP must not be used for longer than the assigned BUD or 28 days, whichever is shorter. This time limit for entering or puncturing is not intended to restrict the BUD of the final CSP. See *14. Establishing Beyond-Use Dates*

16.2 Use of Compounded Single-Dose CSPs and CSP Stock Solutions

When a compounded single-dose CSP or CSP stock solution is used as a component to compound additional CSPs, the original compounded single-dose CSP or CSP stock solution must be entered or punctured in ISO Class 5 or cleaner air and must be stored under the conditions upon which its BUD is based (e.g., refrigerator or controlled room temperature). The component CSP may be used for sterile compounding for up to 12 h or its assigned BUD, whichever is shorter, and any remainder must be discarded. This time limit for entering or puncturing is not intended to restrict the BUD of the final CSP. See *14. Establishing Beyond-Use Dates*.

17. SOPs

Facilities that prepare CSPs must develop SOPs for the compounding process and other support activities. SOPs must include the types of CSPs that are prepared (i.e., Category 1, Category 2, Category 3). A designated person(s) must ensure that SOPs are appropriate and are implemented, which includes ensuring that personnel demonstrate competency in performing every procedure that relates to their job function. A designated person(s) must follow up to ensure that corrective actions are taken if problems, deviations, failures, or errors are identified. The corrective action must be documented.

All personnel who perform or oversee compounding or support activities must be trained in the SOPs. All compounding personnel must be trained to:

- Recognize potential problems, deviations, failures, or errors associated with preparing a CSP (e.g., those related to equipment, facilities, materials, personnel, the compounding process, or testing) that could potentially result in contamination or other adverse impact on CSP quality
- Report any problems, deviations, failures, or errors to the designated person(s)

SOPs must be reviewed initially and at least every 12 months by the designated person(s) to ensure that they reflect current practices, and the review must be documented. Any changes or alterations to an SOP must be made only by a designated person(s) and must be documented. Revisions to SOPs must be communicated to all personnel involved in these processes and procedures, and personnel should document acknowledgment of the communication.

18. QUALITY ASSURANCE AND QUALITY CONTROL

QA is a system of procedures, activities, and oversight that ensures that the compounding process consistently meets quality standards. QC is the sampling, testing, and documentation of results that, taken together, ensure that specifications have been met before release of the CSP. See *Quality Assurance in Pharmaceutical Compounding* ⟨1163⟩.

A facility's QA and QC programs must be formally established and documented in the facility's SOPs that ensure that all aspects of the preparation of CSPs are conducted in accordance with the requirements in this chapter (⟨797⟩) and the laws and regulations of the applicable regulatory jurisdiction. Designated person(s) must ensure that the facility has formal, written QA and QC programs that establish a system of:

1. Adherence to procedures
2. Prevention and detection of errors and other quality problems
3. Evaluation of complaints and adverse events
4. Appropriate investigations and corrective actions

The facility's SOPs must describe the roles, duties, and training of the personnel responsible for each aspect of the QA program. Designated person(s) responsible for the QA program must have the training, experience, responsibility, and authority to perform these duties. The overall QA and QC program must be reviewed at least once every 12 months by the designated person(s). The results of the review must be documented, and appropriate action must be taken if needed.

18.1 Notification About and Recall of Out-of-Specification Dispensed CSPs

If a CSP is dispensed or administered before the results of release testing are known, the facility must have procedures in place to:

- Immediately notify the prescriber of a failure of specifications with the potential to cause patient harm (e.g., sterility, strength, purity, bacterial endotoxin, or other quality attributes)
- Recall any unused dispensed CSPs and quarantine any stock remaining in the pharmacy
- Investigate if other lots are affected and recall if necessary

An SOP for recall of out-of-specification dispensed CSPs must contain:

- Procedures to determine the severity of the problem and the urgency for implementation and completion of the recall
- Procedures to determine the distribution of any affected CSP, including the date and quantity of distribution
- Procedures to identify patients who have received the CSP
- Procedures for disposal and documentation of the recalled CSP
- Procedures to investigate and document the reason for failure

The sterile compounding facility must document the implementation of the recall procedures. The recall must be reported to appropriate regulatory bodies as required by laws and regulations of the applicable regulatory jurisdiction.

18.2 Complaint Handling

Compounding facilities must develop and implement SOPs for handling complaints. Complaints may include but are not limited to concerns or reports on the quality, labeling, or possible adverse reactions related to a specific CSP.

A designated person(s) must review all complaints to determine whether the complaint indicates a potential quality problem with the CSP. If it does, a thorough investigation into the cause of the problem must be initiated and completed. The investigation must consider whether the quality problem extends to other CSPs. Corrective action, if necessary, must be implemented for all potentially affected CSPs.

Consider whether to initiate a recall of potentially affected CSPs and whether to cease sterile compounding processes until all underlying problems have been identified and corrected.

A readily retrievable written or electronic record of each complaint must be kept by the facility, regardless of the source of the complaint (e.g., email, telephone, or mail). The record must contain the name of the complainant or other unique identifier, the date the complaint was received, the nature of the complaint, and the response to the complaint. In addition, to the extent that the information is known, the following should be recorded: the name and strength of the CSP and the assigned internal identification number (e.g., prescription, order, or lot number).

The record must also include the findings of any investigation and any follow-up. Records of complaints must be easily retrievable for review and evaluation for possible trends and must be retained in accordance with the record-keeping requirements in *20. Documentation*. A CSP that is returned in connection with a complaint must be quarantined until it is destroyed after completion of the investigation and in accordance with laws and regulations of the applicable regulatory jurisdiction.

18.3 Adverse Event Reporting

Adverse events potentially associated with the quality of CSPs must be reported in accordance with the facility's SOPs and all laws and regulations of the applicable regulatory jurisdiction. If the investigation into an adverse event reveals a quality problem with a CSP that is likely to affect other patients, those patients and prescribers potentially affected must be informed.

19. CSP HANDLING, STORAGE, PACKAGING, SHIPPING, AND TRANSPORT

Processes and techniques for handling, storing, packaging, and transporting CSPs must be outlined in the facility's SOPs. Personnel who will be handling, storing, packaging, and transporting CSPs within the facility must be trained in accordance with the relevant SOPs, and the training must be documented.

19.1 Handling and Storing CSPs

CSPs must be handled in a manner that maintains CSP quality and packaging integrity. To help ensure that CSP quality is maintained during storage at the compounding facility, personnel must monitor conditions in the storage areas. A controlled temperature area (see ⟨659⟩) must be established and monitored to ensure that the temperature remains within the appropriate range for the CSP. The temperature must be monitored each day, either manually or by a continuous recording device. The results of the temperature readings must be documented in a temperature log per facility SOPs or stored in the continuous temperature recording device and must be retrievable. Temperature monitoring devices must be verified for accuracy at least every 12 months or as required by the manufacturer.

The compounding facility must detect and minimize temperature excursions that are outside the temperature limits within the controlled temperature areas. When it is known that a CSP has been exposed to temperatures either below or above the storage temperature limits for the CSP, a designated person(s) must determine (e.g., by consulting literature or analytical testing) whether the CSP is expected to retain its integrity or quality. If this cannot be determined, it must be discarded.

19.2 Packaging of CSPs

Packaging materials should protect CSPs from damage, leakage, contamination, degradation, and adsorption while preventing inadvertent exposure to transport personnel. The facility must select appropriate shipping containers and packaging materials based on the product specifications, information from vendors, and the mode of transport.

Alternative modes of transport and/or special packaging (e.g., tamper-evident closures) may be needed to protect the quality of CSPs. If the CSP is sensitive to light, light-resistant packaging materials must be used. In some cases, the CSP must be packaged in a special container (e.g., a cooler) to protect it from temperature fluctuations.

19.3 Shipping and Transporting CSPs

Compounding personnel must select modes of transport that are expected to deliver properly packed CSPs in an undamaged, sterile, and stable condition. Inappropriate transport can adversely affect the quality of CSPs. For example, preparation-specific considerations should be given to physical shaking that might occur during pneumatic tube transport or undue exposure to heat, cold, or light. When shipping or transporting CSPs that require special handling (e.g., CSPs with stability concerns), personnel must include specific handling instructions on the exterior of the container.

20. DOCUMENTATION

All facilities where CSPs are prepared must have and maintain written or electronic documentation to demonstrate compliance with the requirements in this chapter. This documentation must include, but is not limited to, the following:

- Personnel training, competency assessments, and qualification records including corrective actions for any failures
- Certification reports, including corrective actions for any failures
- Environmental air and surface monitoring procedures and results
- Equipment records (e.g., calibration, verification, and maintenance reports)
- Receipt of components
- SOPs, MFRs (if required), and CRs (if required)
- Release inspection and testing records
- Information related to complaints and adverse events including corrective actions taken
- Results of investigations and corrective actions

Documentation must comply with all laws and regulations of the applicable regulatory jurisdiction. Records must be legible and stored in a manner that prevents their deterioration and/or loss. All required documentation for a particular CSP (e.g., MFR, CR, and release inspection and testing results) must be readily retrievable for at least 2 years after preparation or as required by laws and regulations of the applicable regulatory jurisdiction or accrediting organization(s), whichever is longer.

21. COMPOUNDING ALLERGENIC EXTRACTS

Licensed allergenic extracts are mixed and diluted into prescription sets for an individual patient, even though these allergenic extract combinations are not specified in the approved licenses for the licensed biological products (e.g., Biological License Applications [BLA]).

Allergenic extract prescription sets must follow standards at least as stringent as those in this section as follows:

21.1 Personnel Qualifications for Compounding Allergenic Extract Prescription Sets

- A designated person(s) with training and expertise in allergen immunotherapy is responsible for ensuring that personnel who will be preparing allergenic extract prescription sets are trained, evaluated, and supervised.
- Before beginning to independently prepare allergenic extracts, all compounding personnel must complete training and be able to demonstrate knowledge of principles and skills for sterile compounding.
- Annual personnel training and competency must be documented. Personnel must demonstrate knowledge and competency in these procedures by passing written or electronic testing before they can be allowed to compound allergenic extract prescription sets.
- Before being allowed to independently compound, all compounders must successfully complete gloved fingertip and thumb sampling on both hands (see *Box 1* and *Table 1*) no fewer than 3 separate times. Each fingertip and thumb evaluation must occur after performing separate and complete hand hygiene and garbing procedures. After the initial competency evaluation, compounding personnel must successfully complete gloved fingertip and thumb sampling on both hands at least every 12 months thereafter.

- Compounding personnel must have their sterile technique and related practices evaluated at least every 12 months as demonstrated by successful completion of a media-fill test (see *Box 2*). If compounding outside of a PEC, the post-media-fill surface sample is not required.
- Personnel who fail competency evaluations must successfully pass reevaluations in the deficient area(s) before they can resume compounding of allergenic extract prescription sets. The designated person(s) must identify the cause of failure and determine appropriate retraining requirements.
- Personnel who have not compounded an allergenic extract prescription set in more than 6 months must be evaluated in all core competencies before resuming compounding duties.

21.2 Personnel Hygiene and Garbing for Compounding Allergenic Extract Prescription Sets

- Before beginning compounding of allergenic extract prescription sets, personnel must perform hand hygiene (see *Box 3*) and garbing procedures according to the facility's SOPs.
- The minimum garb requirements include:
  - A low-lint garment with sleeves that fit snugly around the wrists and an enclosed neck (e.g., gowns)
  - A low-lint, disposable head cover that covers the hair and ears and, if applicable, a disposable cover for facial hair
  - Face mask
  - Sterile powder-free gloves
- Throughout the compounding process, personnel must apply sterile 70% IPA onto all surfaces of the gloves and allow them to dry thoroughly.

21.3 Facilities for Compounding Allergenic Extract Prescription Sets

- The compounding process must occur in an ISO Class 5 PEC or in a dedicated allergenic extract compounding area (AECA). The PEC or AECA used to compound allergenic extract prescription sets must be located away from unsealed windows, doors that connect to the outdoors, and traffic flow, all of which may adversely affect the air quality. Neither a PEC nor an AECA may be located where environmental control challenges (e.g., restrooms, warehouses, or food preparation areas) could negatively affect the air quality. The PEC or the work surfaces in the AECA must be located at least 1 m away from a sink. The impact of activities that will be conducted around or adjacent to the PEC or AECA must be considered carefully when designing such an area.
- If used, the PEC must be certified at least every 6 months (see *5. Certification and Recertification*).
- If used, a visible perimeter must define the AECA.
  - Access to the AECA during compounding must be restricted to authorized personnel.
  - During compounding activities, no other activity is permitted in the AECA.
  - The surfaces of walls, floors, fixtures, shelving, counters, and cabinets in the AECA must be cleanable.
  - Carpet is not allowed in the AECA.
  - Surfaces should be resistant to damage by cleaning and disinfecting agents.
  - The surfaces in the AECA upon which the allergenic extract prescription sets are prepared must be smooth, impervious, free from cracks and crevices, and non-shedding to allow for easy cleaning and disinfecting.
  - Dust-collecting overhangs such as utility pipes, ledges, and windowsills should be minimized. If overhangs or ledges are present, they must be easily cleanable.
  - The AECA must be designed and controlled to provide a well-lighted working environment, with temperature and humidity controls for the comfort of compounding personnel wearing the required garb.

21.4 Cleaning and Disinfecting for Compounding Allergenic Extract Prescription Sets

- In a PEC, all interior surfaces of the PEC must be cleaned and disinfected each day of use before compounding begins and when surface contamination is known or suspected. Apply sterile 70% IPA to the horizontal work surface between each prescription set.
- In an AECA, all work surfaces in the AECA where direct compounding is occurring must be cleaned and disinfected each day of use before compounding begins and when surface contamination is known or suspected. Apply sterile 70% IPA to the horizontal work surface between each prescription set.
  - If present, walls, doors, and door frames within the perimeter of the AECA must be cleaned and disinfected monthly and when surface contamination is known or suspected.
  - Ceilings within the perimeter of the AECA must be cleaned and disinfected when visibly soiled and when surface contamination is known or suspected.
- Vial stoppers on packages of conventionally manufactured sterile ingredients must be wiped with sterile 70% IPA to ensure that the critical sites are wet and allowed to dry before they are used to compound allergenic extract prescription sets.

21.5 Establishing BUDs for Allergenic Extract Prescription Sets

- The BUD for the prescription set must be no later than the earliest expiration date of any allergenic extract or any diluent that is part of the prescription set, and the BUD must not exceed 1 year from the date the prescription set is mixed or diluted.

21.6 Labeling for Allergenic Extract Prescription Sets

- The label of each vial of an allergenic extract prescription set must display the following prominently and understandably:
  - Patient name
  - Type and fractional dilution of each vial, with a corresponding vial number
  - BUD
  - Storage conditions

21.7 Shipping and Transporting Allergenic Extract Prescription Sets

- If shipping or transporting allergenic extract prescription sets, compounding personnel must select modes of transport that are expected to deliver properly packed prescription sets in an undamaged, sterile, and stable condition. Inappropriate transport can adversely affect the quality of allergenic extract prescription sets.
- When shipping or transporting allergenic extract prescription sets that require special handling, personnel must include specific handling instructions on the exterior of the container.

21.8 Documentation for Compounding Allergenic Extract Prescription Sets

- All facilities where allergenic extract prescription sets are prepared must have and maintain written or electronic documentation to include, but not limited to, the following:
  - SOPs describing all aspects of the compounding process
  - Personnel training records, competency assessments, and qualification records including corrective actions for any failures
  - Certification reports of the PEC, if used, including corrective actions for any failures
  - Temperature logs for refrigerator(s)
  - CRs for individual allergenic extract prescription sets (see *Box 10*)
  - Information related to complaints and adverse events including corrective actions taken
  - Investigations and corrective actions

GLOSSARY

ACD: Automated compounding device.
ACPH: Air changes per hour.
Active pharmaceutical ingredient (API): Any substance or mixture of substances intended to be used in the compounding of a preparation, thereby becoming the active ingredient in that preparation and furnishing pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease in humans and animals or affecting the structure and function of the body. Also referred to as *Bulk drug substance*. A conventionally manufactured drug product is not an API but is typically manufactured from an API(s).
Added substance: An ingredient that is necessary to compound a preparation but is not intended or expected to cause a pharmacologic response if administered alone in the amount or concentration contained in a single dose of the compounded preparation. The term is used synonymously with the terms *inactive ingredient*, *excipient*, and *pharmaceutical ingredient*.
Administration: The direct application of a sterile product or preparation to a single patient by injecting, infusing, or otherwise providing a sterile product or preparation in its final form.
Airlock: A space with interlocked doors, constructed to maintain air pressure control when items move between two adjoining areas (generally with different air cleanliness standards). The intent of an airlock is to prevent ingress of particulate matter and microbial contamination from a lesser-controlled area.
Alcohol-based hand rub: An alcohol-containing preparation (liquid, gel, or foam) designed for application to the hands of healthcare personnel to inactivate microorganisms and/or temporarily suppress their growth. Such preparations may contain one or more types of alcohol, other active ingredients, excipients, and humectants.
Allergenic extract: A biological substance used for the diagnosis and/or treatment of allergic diseases such as allergic rhinitis, allergic sinusitis, allergic conjunctivitis, bee venom allergy, and food allergy.
Allergenic extract compounding area (AECA): A designated space, area, or room that is not required to be classified, with a visible perimeter that is suitable for preparation of allergenic extract prescription sets.
Allergenic extract prescription set: Combinations of licensed allergenic extracts that would be mixed and diluted to provide subcutaneous immunotherapy to an individual patient, even though these allergenic extract combinations are not specified in the approved BLAs for the licensed biological products.
Anteroom: An ISO Class 8 or cleaner room with fixed walls and doors where personnel hand hygiene, garbing procedures, and other activities that generate high particulate levels may be performed. The anteroom is the transition room between the unclassified area of the facility and the buffer room.
Aseptic processing: A method by which separate, sterile components (e.g., drugs, containers, or closures) are brought together under conditions that maintain their sterility. The components can either be purchased as sterile or, when starting with nonsterile components, can be separately sterilized prior to combining (e.g., by membrane filtration or by autoclave).
Aseptic technique: A set of methods used to keep objects and areas free of microorganisms and thereby minimize infection risk to the patient. It is accomplished through practices that maintain the microbe count at an irreducible minimum.
Assigned trainer: One or more individuals assigned by the designated person(s) to be responsible and accountable for directly providing the training, observation, and/or evaluation of personnel for the preparation of CSPs.
Batch: More than one CSP prepared as described in the MFR in a single, discrete process, and expected to have uniform character and quality, within specified limits.
Beyond-use date (BUD): The date, or hour and the date, after which a CSP must not be used, stored, or transported. The date is determined from the date and time the preparation is compounded.
Biological safety cabinet (BSC): A ventilated cabinet that may be used for compounding. These cabinets are divided into three general classes (Class I, Class II, and Class III). Class II BSCs are further divided into types (Type A1, Type A2, Type B1, Type B2, and Type C1).
Biological safety cabinet (BSC), Class II: A ventilated cabinet with an open front and inward and downward unidirectional HEPA-filtered airflow and HEPA-filtered exhaust. A BSC used to prepare a CSP must be capable of providing an ISO Class 5 or better environment for preparation of the CSPs.
BLA: Biological license application.

Blood components: Any therapeutic constituent of blood separated by physical or mechanical means (e.g., white cells, red cells, platelets, plasma, serum). It is not intended to include plasma-derived products (e.g., albumin, coagulation factors, immunoglobulins) manufactured under an approved BLA or equivalent.
BMBL: Biosafety in Microbiological and Biomedical Laboratories.
Buffer room: An ISO Class 7 or cleaner room with fixed walls and doors where PEC(s) that generate and maintain an ISO Class 5 environment are physically located. The buffer room may only be accessed through the anteroom or another buffer room.
Bulk drug substance: See the entry for *Active pharmaceutical ingredient*.
Category 1 CSP: A CSP that is assigned a BUD of 12 h or less at controlled room temperature or 24 h or less refrigerated that is compounded in accordance with all applicable requirements for Category 1 CSPs in this chapter.
Category 2 CSP: A CSP that may be assigned a BUD of greater than 12 h at controlled room temperature or greater than 24 h refrigerated that is compounded in accordance with all applicable requirements for Category 2 CSPs in this chapter.
Category 3 CSP: A CSP that may be assigned a BUD exceeding the limits in *Table 13* for Category 2 CSPs and is compounded in accordance with all applicable requirements for Category 3 CSPs in this chapter.
CDC: Centers for Disease Control and Prevention.
Certificate of analysis (COA): A report from the supplier of a component, container, or closure that accompanies the supplier's material and contains the specifications and results of all analyses and a description of the material.
CFU: Colony-forming units.
Classified area: An area that maintains an air quality classification based on the ISO standards required in this chapter (see also the definition for *ISO class*).
Cleaning: The process of removing substances (e.g., organic and inorganic material) from objects and surfaces, normally accomplished by manually or mechanically using water with detergents or enzymatic products.
Cleaning agent: An agent, usually containing a surfactant, used for the removal of substances (e.g., dirt, debris, microbes, and residual drugs or chemicals) from surfaces.
Cleanroom suite: A classified area that consists of both an anteroom and buffer room.
Component: Any ingredient used in the compounding of a preparation, including any active ingredient, added substance, or conventionally manufactured product.
Compounded sterile preparation (CSP): A preparation intended to be sterile that is created by combining, admixing, diluting, pooling, reconstituting, repackaging, or otherwise altering a drug product or bulk drug substance.
Compounded stock solution: A sterile mixture of components that is used to compound additional CSPs.
Compounding: The process of combining, admixing, diluting, pooling, reconstituting, repackaging, or otherwise altering a drug product or bulk drug substance to create a sterile preparation.
Compounding area: The area where compounding is occurring (i.e., a cleanroom suite, inside the perimeter of the SCA, or AECA).
Compounding aseptic containment isolator (CACI): A type of RABS that uses HEPA filtration to provide an ISO Class 5 unidirectional air environment designed for the compounding of sterile HDs.
Compounding aseptic isolator (CAI): A type of RABS that uses HEPA filtration to provide an ISO Class 5 unidirectional air environment designed for compounding of sterile non-HDs.
Compounding record (CR): Documents the compounding of each CSP.
Container closure system: Packaging components that together contain and protect the dosage form. This includes primary packaging components and secondary packaging components, if the latter are intended to provide additional protection.
Containment glove bag: A single-use disposable glove bag that is capable of containing airborne chemical particles.
Containment ventilated enclosure (CVE): A non-ISO classified full or partial enclosure that uses ventilation principles to capture, contain, and remove airborne contaminants through HEPA filtration and prevent their release into the work environment.
Conventionally manufactured product: A pharmaceutical dosage form, usually the subject of an application approved by the applicable national regulatory agency, that is manufactured under current good manufacturing practice conditions.
Critical site: A location that includes any component or fluid pathway surfaces (e.g., vial septa, injection ports, and beakers) or openings (e.g., opened ampules and needle hubs) that are exposed and at risk of direct contact with air (e.g., ambient room or HEPA filtered), moisture (e.g., oral and mucosal secretions), or touch contamination.
Designated person(s): One or more individuals assigned to be responsible and accountable for the performance and operation of the facility and personnel as related to the preparation of CSPs.
Direct compounding area (DCA): A critical area within the ISO Class 5 PEC where critical sites are exposed to unidirectional HEPA-filtered air, also known as first air.
Disinfectant: A chemical or physical agent used on inanimate surfaces and objects to destroy fungi, viruses, and bacteria. Sporicidal disinfectants are considered a special class of disinfectants that also are effective against bacterial and fungal spores.
Dynamic airflow smoke pattern test: A PEC test in which a visible source of smoke, which is neutrally buoyant, is used to observe air patterns within the unidirectional space (i.e., the DCA) under dynamic operating conditions (see the entry for *Dynamic operating conditions*). This test is not appropriate for ISO Class 7 or ISO Class 8 cleanrooms that do not have unidirectional airflow (see the entry for *Visual smoke study*).
Dynamic operating conditions: Conditions in the compounding area in which operating personnel are present and simulating or performing compounding. The conditions should reflect the largest number of personnel and highest complexity of compounding expected during routine operations as determined by the designated person(s).
ECV: Endotoxin challenge vial.
EPA: US Environmental Protection Agency.
Excipient: See the entry for *Added substance*.
FDA: US Food and Drug Administration.
Filter integrity test: A test (e.g., bubble point test) of the integrity of a sterilizing grade filter performed after the filtration process to detect whether the integrity of the filter has been compromised.
Final yield: The total number of containers actually prepared at the end of the compounding process prior to release testing.

First air: The air exiting the HEPA filter in a unidirectional air stream.
Formulation: The specific qualitative and quantitative composition of the final CSP.
Garb: Items such as gloves, garments (e.g., gowns), shoe covers, head and facial hair covers, masks, and other items designed to reduce particle-shedding from personnel and minimize the risk of contamination of CSP(s).
GFT: Gloved fingertip and thumb sampling.
Hazardous drug (HD): Any drug identified by at least one of the following six criteria: carcinogenicity, teratogenicity or developmental toxicity, reproductive toxicity in humans, organ toxicity at low dose in humans or animals, genotoxicity, or new drugs that mimic existing HDs in structure or toxicity.
High-efficiency particulate air (HEPA) filtration: Being, using, or containing a filter designed to remove 99.97% of airborne particles measuring 0.3-micron or greater in diameter passing through it.
HVAC: Heating, ventilation, and air conditioning.
Integrated vertical laminar flow zone (IVLFZ): A designated ISO Class 5 area serving as the PEC within an ISO Class 7 or cleaner buffer room. In the IVLFZ, unidirectional airflow is created by placing HEPA filters over the entire surface of the worktables and by effective placement of air returns.
IPA: Isopropyl alcohol.
ISO: International Organization for Standardization.
ISO class: An air-quality classification from the International Organization for Standardization.
Label: The part of the labeling on the immediate container.
Labeling: All labels and other written, printed, or graphic matter on the immediate container or on or inside any packaging system or wrapper in which the article is enclosed, except any outer shipping container.
Laminar airflow system (LAFS): A device or zone within a buffer room that provides an ISO Class 5 or better air quality environment for sterile compounding. The system provides a unidirectional HEPA-filtered airflow.
Laminar airflow workbench (LAFW): A device that is a type of LAFS that provides an ISO Class 5 or better air quality environment for sterile compounding. The device provides a unidirectional HEPA-filtered airflow.
Line of demarcation: A visible line on the floor that separates the clean and dirty sides of the anteroom.
Low-lint wiper: A wiper exhibiting few, if any, fibers or other contamination, visible without magnification, which is separate from, or easily removed from, the wiper material in a dry condition.
Master formulation record (MFR): A detailed record of procedures that describes how the CSP is to be prepared.
MEA: Malt extract agar.
Media-fill test: A simulation used to qualify processes and personnel engaged in sterile compounding to ensure that the processes and personnel are able to prepare CSPs without contamination.
Monograph: A quality documentary standard within *USP–NF* that articulates the quality expectations for a medicine including for its identity, strength, purity, and performance. It also describes the tests to validate that a medicine and its ingredients meet these criteria.
Multiple-dose container: A container of sterile product for parenteral administration (e.g., injection or infusion) that is designed to contain more than one dose of the sterile product. A multiple-dose container is usually required to meet the antimicrobial effectiveness testing criteria. See ⟨659⟩, *Injection Packaging Systems, Multiple-dose container*.
One-step disinfectant cleaner: A product with an EPA-registered (or equivalent) claim that it can clean and disinfect a nonporous surface in the presence of light to moderate organic soiling without a separate cleaning step.
Oversight: The review, monitoring, and supervision of actions taken by personnel, bearing responsibility for those actions, and being available for consultation if and when needed even if not physically present.
Pass-through chamber: An enclosure with sealed doors on both sides that should be interlocked. The pass-through chamber is positioned between two spaces for the purpose of minimizing particulate transfer while moving materials from one space to another.
Perimeter: A visible demarcation (such as a door, walls, or visible marking on the floor) that defines the SCA or AECA.
Pharmaceutical isolator: An enclosure that provides HEPA-filtered ISO Class 5 unidirectional air operated at a continuously higher pressure than its surrounding environment and is decontaminated using an automated system. It uses only decontaminated interfaces or rapid transfer ports for materials transfer. [NOTE—A CAI or CACI is not a pharmaceutical isolator.]
Pharmacy bulk package: A conventionally manufactured sterile product for parenteral use that contains many single doses intended for use in a pharmacy admixture program. A pharmacy bulk package may either be used to prepare admixtures for infusion or, through a sterile transfer device, for filling sterile containers. See ⟨659⟩, *Injection Packaging Systems, Pharmacy bulk package*.
Positive-pressure room: A room that is maintained at higher pressure than the adjacent spaces, and therefore the net airflow is out of the room.
PPE: Personal protective equipment.
Preservative: A substance added to inhibit microbial growth.
Primary engineering control (PEC): A device or zone that provides an ISO Class 5 air quality environment for sterile compounding.
Probability of a nonsterile unit (PNSU): The probability of an item being nonsterile after it has been exposed to a verified sterilization process. A PNSU value can only be applied to terminal sterilization. [NOTE—This is also called the sterility assurance level (SAL).]
Pyrogen: A substance that induces a febrile reaction in a patient.
Quality assurance (QA): A system of procedures, activities, and oversight that ensures that the compounding process consistently meets quality standards.
Quality control (QC): The sampling, testing, and documentation of results that, taken together, ensure that specifications have been met before release of the CSP.
Reconstitution: The process of adding a diluent to a conventionally manufactured product to prepare a sterile solution or suspension.

Release inspection and testing: Visual inspection and testing performed to ensure that a preparation meets appropriate quality characteristics.

Repackaging: The act of removing a sterile product or preparation from its original primary container and placing it into another primary container, usually of smaller size without further manipulation.

Restricted-access barrier system (RABS): An enclosure that provides HEPA-filtered ISO Class 5 unidirectional air that allows for the ingress and/or egress of materials through defined openings that have been designed and validated to preclude the transfer of contamination, and that generally are not to be opened during operations. Examples of RABS include CAIs and CACIs.

SDA: Sabouraud dextrose agar.

Secondary engineering control (SEC): The area where the PEC is placed (e.g., a cleanroom suite or an SCA). It incorporates specific design and operational parameters required to minimize the risk of contamination within the compounding area.

Segregated compounding area (SCA): A designated space, area, or room that is not required to be classified and is defined with a visible perimeter. The SCA must contain a PEC and is suitable for preparation of Category 1 CSPs only.

Single-dose containers: A container of sterile product for parenteral administration (e.g., injection or infusion) that is designed for use with a single patient as a single injection/infusion. A single-dose container usually does not contain a preservative. See ⟨659⟩*, Injection Packaging Systems, Single-dose container*.

SOP: Standard operating procedure.

Specification: The tests, analytical methods, and acceptance criteria to which any component, CSP, container closure system, equipment, or other material used in compounding CSPs must conform to be considered acceptable for its intended use.

Sporicidal disinfectant: A chemical or physical agent that destroys bacterial and fungal spores when used in sufficient concentration for a specified contact time. It is expected to kill all vegetative microorganisms.

Stability: The extent to which a product or preparation retains physical and chemical properties and characteristics within specified limits throughout its expiration or BUD.

Sterility: The absence of viable microorganisms.

Sterility assurance level (SAL): See the entry for *Probability of a nonsterile unit* (PNSU).

Sterilization by filtration: Passage of a gas or liquid through a sterilizing-grade membrane to yield filtrates that are sterile.

Sterilizing-grade filter: Filter membranes that are documented to retain 100% of a culture of 10^7 microorganisms of a strain of *Brevundimonas diminuta* per square centimeters of membrane surface under a pressure of not less than 30 psi. Such filter membranes are nominally 0.22- or 0.2-µm pore size.

Terminal sterilization: The application of a lethal process (e.g., steam, dry heat, irradiation) to sealed containers for the purpose of achieving a predetermined PNSU of greater than 10^{-6} or a probability of less than one in one million of a nonsterile unit.

TSA: Trypticase soy agar.

Unclassified space: A space not required to meet any air cleanliness classification based on the ISO.

Unidirectional airflow: Air within a PEC moving in a single direction in a uniform manner and at sufficient velocity to sweep particles away from the DCA.

Verify: To confirm that a method, process, system, or equipment will perform as expected under the conditions of actual use.

Visual smoke study: A test, used in ISO Class 7 and ISO Class 8 rooms that do not have unidirectional airflow, in which a visible source of smoke, which is neutrally buoyant, is used to verify an absence of stagnant airflow. This test does not need to be performed under dynamic operating conditions and is not appropriate for PECs (see the entry for *Dynamic airflow smoke pattern test*).

Workflow management system: Technology comprised of hardware and/or software that allows for automation to assist in the verification of components of, and preparation of, CSPs and to document components and processes.▲ (Official 1-Nov-2023)

⟨800⟩ HAZARDOUS DRUGS—HANDLING IN HEALTHCARE SETTINGS

1. INTRODUCTION AND SCOPE

This chapter describes practice and quality standards for handling hazardous drugs (HDs) to promote patient safety, worker safety, and environmental protection. Handling HDs includes, but is not limited to, the receipt, storage, compounding, dispensing, administration, and disposal of sterile and nonsterile products and preparations.

This chapter applies to all healthcare personnel who handle HD preparations and all entities that store, prepare, transport, or administer HDs (e.g., pharmacies, hospitals and other healthcare institutions, patient treatment clinics, physicians' practice facilities, or veterinarians' offices). Personnel who may potentially be exposed to HDs include, but are not limited to: pharmacists, pharmacy technicians, nurses, physicians, physician assistants, home healthcare workers, veterinarians, and veterinary technicians.

Entities that handle HDs must incorporate the standards in this chapter into their occupational safety plan. The entity's health and safety management system must, at a minimum, include:

- A list of HDs
- Facility and engineering controls
- Competent personnel
- Safe work practices
- Proper use of appropriate Personal Protective Equipment (PPE)
- Policies for HD waste segregation and disposal

The chapter is organized into the following main sections:

1. Introduction and Scope
2. List of Hazardous Drugs
3. Types of Exposure
4. Responsibilities of Personnel Handling Hazardous Drugs
5. Facilities and Engineering Controls
6. Environmental Quality and Control
7. Personal Protective Equipment
8. Hazard Communication Program
9. Personnel Training
10. Receiving
11. Labeling, Packaging, Transport, and Disposal
12. Dispensing Final Dosage Forms
13. Compounding
14. Administering
15. Deactivating, Decontaminating, Cleaning, and Disinfecting
16. Spill Control
17. Documentation and Standard Operating Procedures
18. Medical Surveillance

Glossary

Appendices

- Appendix 1: Acronyms
- Appendix 2: Examples of Designs for Hazardous Drug Compounding Areas
- Appendix 3: Types of Biological Safety Cabinets

References

Change to read:

2. LIST OF HAZARDOUS DRUGS

The National Institute for Occupational Safety and Health (NIOSH) maintains a list of antineoplastic and other HDs used in healthcare. ▲For the purposes of this chapter, the term antineoplastic only refers to antineoplastic drugs included in Table 1 of the most current NIOSH List.▲ (RB 1-Jul-2020) An entity must maintain a list of HDs, which must include any items on the current NIOSH list that the entity handles. The entity's list must be reviewed at least every 12 months. Whenever a new agent or dosage form is used, it should be reviewed against the entity's list.

The NIOSH list of antineoplastic and other HDs provides the criteria used to identify HDs. These criteria must be used to identify HDs that enter the market after the most recent version of the NIOSH list, or that the entity handles as an investigational drug. If the information available on a drug is deemed insufficient to make an informed decision, consider the drug hazardous until more information is available.

Box 1: Containment Requirements

- Drugs on the NIOSH list that must follow the requirements in this chapter include:
  - Any HD API
  - Any antineoplastic requiring HD manipulation
- Drugs on the NIOSH list that do not have to follow all the containment requirements of this chapter if an assessment of risk is performed and implemented include:
  - Final dosage forms of compounded HD preparations and conventionally manufactured HD products, including antineoplastic dosage forms that do not require any further manipulation other than counting or repackaging (unless required by the manufacturer)
- For dosage forms of other HDs on the NIOSH list, the entity may perform an assessment of risk to determine alternative containment strategies and/work practices

Some dosage forms of drugs defined as hazardous may not pose a significant risk of direct occupational exposure because of their dosage formulation (e.g., tablets or capsules—solid, intact medications that are administered to patients without modifying the formulation). However, dust from tablets and capsules may present a risk of exposure by skin contact and/or inhalation. An assessment of risk may be performed for these dosage forms to determine alternative containment strategies and/or work practices. If an assessment of risk is not performed, all HDs must be handled with all containment strategies defined in this chapter.

The assessment of risk must, at a minimum, consider the following:

- Type of HD (e.g., antineoplastic, non-antineoplastic, reproductive risk only)
- Dosage form
- Risk of exposure
- Packaging
- Manipulation

If an assessment of risk approach is taken, the entity must document what alternative containment strategies and/or work practices are being employed for specific dosage forms to minimize occupational exposure. If used, the assessment of risk must be reviewed at least every 12 months and the review documented.

3. TYPES OF EXPOSURE

Routes of unintentional entry of HDs into the body include dermal and mucosal absorption, inhalation, injection, and ingestion (e.g., contaminated foodstuffs, spills, or mouth contact with contaminated hands). Containers of HDs have been shown to be contaminated upon receipt. Both clinical and nonclinical personnel may be exposed to HDs when they handle HDs or touch contaminated surfaces. *Table 1* lists examples of potential routes of exposure based on activity.

Table 1. Examples of Potential Opportunities of Exposure Based on Activity

Activity	Potential Opportunity of Exposure
Receipt	• Contacting HD residues present on drug containers, individual dosage units, outer containers, work surfaces, or floors
Dispensing	• Counting or repackaging tablets and capsules
Compounding and other manipulations	• Crushing or splitting tablets or opening capsules • Pouring oral or topical liquids from one container to another • Weighing or mixing components • Constituting or reconstituting powdered or lyophilized HDs • Withdrawing or diluting injectable HDs from parenteral containers • Expelling air or HDs from syringes • Contacting HD residue present on PPE or other garments • Deactivating, decontaminating, cleaning, and disinfecting areas contaminated with or suspected to be contaminated with HDs • Maintenance activities for potentially contaminated equipment and devices
Administration	• Generating aerosols during administration of HDs by various routes (e.g., injection, irrigation, oral, inhalation, or topical application) • Performing certain specialized procedures (e.g., intraoperative intraperitoneal injection or bladder instillation) • Priming an IV administration set
Patient-care activities	• Handling body fluids (e.g., urine, feces, sweat, or vomit) or body-fluid-contaminated clothing, dressings, linens, and other materials
Spills	• Spill generation, management, and disposal
Transport	• Moving HDs within a healthcare setting
Waste	• Collection and disposal of hazardous waste and trace contaminated waste

4. RESPONSIBILITIES OF PERSONNEL HANDLING HAZARDOUS DRUGS

Each entity must have a designated person who is qualified and trained to be responsible for developing and implementing appropriate procedures; overseeing entity compliance with this chapter and other applicable laws, regulations, and standards; ensuring competency of personnel; and ensuring environmental control of the storage and compounding areas. The designated

person must thoroughly understand the rationale for risk-prevention policies, risks to themselves and others, risks of non-compliance that may compromise safety, and the responsibility to report potentially hazardous situations to the management team. The designated person must also be responsible for the oversight of monitoring the facility and maintaining reports of testing/sampling performed in facilities, and acting on the results.

All personnel who handle HDs are responsible for understanding the fundamental practices and precautions and for continually evaluating these procedures and the quality of final HDs to prevent harm to patients, minimize exposure to personnel, and minimize contamination of the work and patient-care environment.

5. FACILITIES AND ENGINEERING CONTROLS

HDs must be handled under conditions that promote patient safety, worker safety, and environmental protection. Signs designating the hazard must be prominently displayed before the entrance to the HD handling areas. Access to areas where HDs are handled must be restricted to authorized personnel to protect persons not involved in HD handling. HD handling areas must be located away from breakrooms and refreshment areas for personnel, patients, or visitors to reduce risk of exposure.

Designated areas must be available for:

- Receipt and unpacking
- Storage of HDs
- Nonsterile HD compounding (if performed by the entity)
- Sterile HD compounding (if performed by the entity)

Certain areas are required to have negative pressure from surrounding areas to contain HDs and minimize risk of exposure. Consideration should be given to uninterrupted power sources (UPS) for the ventilation systems to maintain negative pressure in the event of power loss.

5.1 Receipt

Antineoplastic HDs and all HD APIs must be unpacked (i.e., removal from external shipping containers) in an area that is neutral/normal or negative pressure relative to the surrounding areas. HDs must not be unpacked from their external shipping containers in sterile compounding areas or in positive pressure areas.

5.2 Storage

HDs must be stored in a manner that prevents spillage or breakage if the container falls. Do not store HDs on the floor. In areas prone to specific types of natural disasters (e.g., earthquakes) the manner of storage must meet applicable safety precautions, such as secure shelves with raised front lips.

Antineoplastic HDs requiring manipulation other than counting or repackaging of final dosage forms and any HD API must be stored separately from non-HDs in a manner that prevents contamination and personnel exposure. These HDs must be stored in an externally ventilated, negative-pressure room with at least 12 air changes per hour (ACPH). Non-antineoplastic, reproductive risk only, and final dosage forms of antineoplastic HDs may be stored with other inventory if permitted by entity policy.

Sterile and nonsterile HDs may be stored together, but HDs used for nonsterile compounding should not be stored in areas designated for sterile compounding to minimize traffic into the sterile compounding area.

Refrigerated antineoplastic HDs must be stored in a dedicated refrigerator in a negative pressure area with at least 12 ACPH [e.g., storage room, buffer room, or containment segregated compounding area (C-SCA)]. If a refrigerator is placed in a negative pressure buffer room, an exhaust located adjacent to the refrigerator's compressor and behind the refrigerator should be considered.

5.3 Compounding

Engineering controls are required to protect the preparation from cross-contamination and microbial contamination (if preparation is intended to be sterile) during all phases of the compounding process. Engineering controls for containment are divided into three categories representing primary, secondary, and supplementary levels of control. A containment primary engineering control (C-PEC) is a ventilated device designed to minimize worker and environmental HD exposure when directly handling HDs. The containment secondary engineering control (C-SEC) is the room in which the C-PEC is placed. Supplemental engineering controls [e.g., closed-system drug-transfer device (CSTD)] are adjunct controls to offer additional levels of protection. *Appendix 2* provides examples for designs of HD compounding areas.

Sterile and nonsterile HDs must be compounded within a C-PEC located in a C-SEC. The C-SEC used for sterile and nonsterile compounding must:

- Be externally vented
- Be physically separated (i.e., a different room from other preparation areas)
- Have an appropriate air exchange (e.g., ACPH)
- Have a negative pressure between 0.01 and 0.03 inches of water column relative to all adjacent areas

The C-PEC must operate continuously if it supplies some or all of the negative pressure in the C-SEC or if it is used for sterile compounding. If there is any loss of power to the C-PEC, or if repair or moving occurs, all activities occurring in the C-PEC must be suspended immediately. If necessary, protect the unit by covering it appropriately per the manufacturer's recommendations. Once the C-PEC can be powered on, decontaminate, clean, and disinfect (if used for sterile compounding) all surfaces and wait the manufacturer-specified recovery time before resuming compounding.

A sink must be available for hand washing. An eyewash station and/or other emergency or safety precautions that meet applicable laws and regulations must be readily available. Care must be taken to locate water sources and drains in areas where their presence will not interfere with required ISO classifications. Water sources and drains must be located at least 1 meter away from the C-PEC.

For entities that compound both nonsterile and sterile HDs, the respective C-PECs must be placed in separate rooms, unless those C-PECs used for nonsterile compounding are sufficiently effective that the room can continuously maintain ISO 7 classification throughout the nonsterile compounding activity. If the C-PECs used for sterile and nonsterile compounding are placed in the same room, they must be placed at least 1 meter apart and particle-generating activity must not be performed when sterile compounding is in process.

5.3.1 NONSTERILE COMPOUNDING

In addition to this chapter, nonsterile compounding must follow standards in *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩. A C-PEC is not required if manipulations are limited to handling of final dosage forms (e.g., counting or repackaging of tablets and capsules) that do not produce particles, aerosols, or gasses.

The C-PECs used for manipulation of nonsterile HDs must be either externally vented (preferred) or have redundant–HEPA filters in series. Nonsterile HD compounding must be performed in a C-PEC that provides personnel and environmental protection, such as a Class I Biological Safety Cabinet (BSC) or Containment Ventilated Enclosure (CVE). A Class II BSC or a compounding aseptic containment isolator (CACI) may also be used. For occasional nonsterile HD compounding, a C-PEC used for sterile compounding (e.g., Class II BSC or CACI) may be used but must be decontaminated, cleaned, and disinfected before resuming sterile compounding in that C-PEC. A C-PEC used only for nonsterile compounding does not require unidirectional airflow because the critical environment does not need to be ISO classified.

The C-PEC must be placed in a C-SEC that has at least 12 ACPH. *Table 2* summarizes the engineering controls required for nonsterile HD compounding.

Due to the difficulty of cleaning HD contamination, surfaces of ceilings, walls, floors, fixtures, shelving, counters, and cabinets in the nonsterile compounding area must be smooth, impervious, free from cracks and crevices, and non-shedding.

Table 2. Engineering Controls for Nonsterile HD Compounding

C-PEC	C-SEC Requirements
• Externally vented (preferred) or redundant–HEPA filtered in series • Examples: CVE, Class I or II BSC, CACI	• Externally vented • 12 ACPH • Negative pressure between 0.01 and 0.03 inches of water column relative to adjacent areas

5.3.2 STERILE COMPOUNDING

In addition to this chapter, sterile compounding must follow standards in ⟨797⟩.

All C-PECs used for manipulation of sterile HDs must be externally vented. Sterile HD compounding must be performed in a C-PEC that provides an ISO Class 5 or better air quality, such as a Class II or III BSC or CACI. Class II BSC types A2, B1, or B2 are acceptable. For most known HDs, type A2 cabinets offer a simple and reliable integration with the ventilation and pressurization requirements of the C-SEC. Class II type B2 BSCs are typically reserved for use with volatile components. *Appendix 3* describes the different types of BSCs.

A laminar airflow workbench (LAFW) or compounding aseptic isolator (CAI) must not be used for the compounding of an antineoplastic HD. A BSC or CACI used for the preparation of HDs must not be used for the preparation of a non-HD unless the non-HD preparation is placed into a protective outer wrapper during removal from the C-PEC and is labeled to require PPE handling precautions.

The C-PEC must be located in a C-SEC, which may either be an ISO Class 7 buffer room with an ISO Class 7 ante-room (preferred) or an unclassified containment segregated compounding area (C-SCA). If the C-PEC is placed in a C-SCA, the beyond-use date (BUD) of all compounded sterile preparations (CSPs) prepared must be limited as described in ⟨797⟩ for CSPs prepared in a segregated compounding area. *Table 3* summarizes the engineering controls required for sterile HD compounding.

Table 3. Engineering Controls for Sterile HD Compounding

Configuration	C-PEC	C-SEC	Maximum BUD
ISO Class 7 buffer room with an ISO Class 7 ante-room	• Externally vented • Examples: Class II BSC or CACI	• Externally vented • 30 ACPH • Negative pressure between 0.01 and 0.03 inches of water column relative to adjacent areas	As described in ⟨797⟩
Unclassified C-SCA	• Externally vented • Examples: Class II BSC or CACI	• Externally vented • 12 ACPH • Negative pressure between 0.01 and 0.03 inches of water column relative to adjacent areas	As described in ⟨797⟩ for CSPs prepared in a segregated compounding area

ISO Class 7 buffer room with an ISO class 7 ante-room: The C-PEC is placed in an ISO Class 7 buffer room that has fixed walls, HEPA-filtered supply air, a negative pressure between 0.01 and 0.03 inches of water column relative to all adjacent areas and a minimum of 30 ACPH.

The buffer room must be externally vented. Because the room through which entry into the HD buffer room (e.g., ante-room or non-HD buffer room) plays an important role in terms of total contamination control, the following is required:

- Minimum of 30 ACPH of HEPA-filtered supply air
- Maintain a positive pressure of at least 0.02 inches of water column relative to all adjacent unclassified areas
- Maintain an air quality of ISO Class 7 or better

An ISO Class 7 ante-room with fixed walls is necessary to provide inward air migration of equal cleanliness classified air into the negative pressure buffer room to contain any airborne HD. A hand-washing sink must be placed in the ante-room at least 1 meter from the entrance to the HD buffer room to avoid contamination migration into the negative pressure HD buffer room.

Although not a recommended facility design, if the negative-pressure HD buffer room is entered though the positive-pressure non-HD buffer room, the following is also required:

- A line of demarcation must be defined within the negative-pressure buffer room for donning and doffing PPE
- A method to transport HDs, HD CSPs, and HD waste into and out of the negative pressure buffer room to minimize the spread of HD contamination. This may be accomplished by use of a pass-through chamber between the negative-pressure buffer area and adjacent space. The pass-through chamber must be included in the facility's certification to ensure that particles are not compromising the air quality of the negative-pressure buffer room. A refrigerator pass-through must not be used. Other methods of containment (such as sealed containers) may be used.

HD CSPs prepared in an ISO Class 7 buffer room with an ISO Class 7 ante-room may use the BUDs described in ⟨797⟩, based on the categories of CSP, sterility testing, and storage temperature.

Containment segregated compounding area (C-SCA): The C-PEC is placed in an unclassified C-SCA that has fixed walls, a negative pressure between 0.01 and 0.03 inches of water column relative to all adjacent areas, and a minimum of 12 ACPH. The C-SCA must be externally vented. A hand-washing sink must be placed at least 1 meter from C-PEC and may be either inside the C-SCA or directly outside the C-SCA.

Only low- and medium-risk HD CSPs may be prepared in a C-SCA. HD CSPs prepared in the C-SCA must not exceed the BUDs described in ⟨797⟩ for CSPs prepared in a segregated compounding area.

5.4 Containment Supplemental Engineering Controls

Containment supplemental engineering controls, such as CSTDs, provide adjunct controls to offer an additional level of protection during compounding or administration. Some CSTDs have been shown to limit the potential of generating aerosols during compounding. However, there is no certainty that all CSTDs will perform adequately. Until a published universal performance standard for evaluation of CSTD containment is available, users should carefully evaluate the performance claims associated with available CSTDs based on independent, peer-reviewed studies and demonstrated contamination reduction.

A CSTD must not be used as a substitute for a C-PEC when compounding. CSTDs should be used when compounding HDs when the dosage form allows. CSTDs must be used when administering antineoplastic HDs when the dosage form allows. CSTDs known to be physically or chemically incompatible with a specific HD must not be used for that HD.

6. ENVIRONMENTAL QUALITY AND CONTROL

Environmental wipe sampling for HD surface residue should be performed routinely (e.g., initially as a benchmark and at least every 6 months, or more often as needed, to verify containment). Surface wipe sampling should include:

- Interior of the C-PEC and equipment contained in it
- Pass-through chambers
- Surfaces in staging or work areas near the C-PEC
- Areas adjacent to C-PECs (e.g., floors directly under C-PEC, staging, and dispensing area)
- Areas immediately outside the HD buffer room or the C-SCA
- Patient administration areas

There are currently no studies demonstrating the effectiveness of a specific number or size of wipe samples in determining levels of HD contamination. Wipe sampling kits should be verified before use to ensure the method and reagent used have been tested to recover a specific percentage of known marker drugs from various surface types found in the sampled area. There are currently no certifying agencies for vendors of wipe sample kits.

There is currently no standard for acceptable limits for HD surface contamination. Common marker HDs that can be assayed include cyclophosphamide, ifosfamide, methotrexate, fluorouracil, and platinum-containing drugs. An example of measurable contamination would be cyclophosphamide levels >1.00 ng/cm^2, which were shown in some studies to result in uptake of the drug in exposed workers. If any measurable contamination is found, the designated person must identify, document, and contain the cause of contamination. Such action may include reevaluating work practices, re-training personnel, performing thorough deactivation, decontamination, cleaning, and improving engineering controls. Repeat the wipe sampling to validate that the deactivation/decontamination and cleaning steps have been effective.

7. PERSONAL PROTECTIVE EQUIPMENT

Personal Protective Equipment (PPE) provides worker protection to reduce exposure to HD aerosols and residues. Additional PPE may be required to handle the HDs outside of a C-PEC, such as treating a patient or cleaning a spill. The NIOSH list of antineoplastic and other HDs provides general guidance on PPE for possible scenarios that may be encountered in healthcare settings. Disposable PPE must not be re-used. Reusable PPE must be decontaminated and cleaned after use.

Gowns, head, hair, shoe covers, and two pairs of chemotherapy gloves are required for compounding sterile and nonsterile HDs. Two pairs of chemotherapy gloves are required for administering injectable antineoplastic HDs. Gowns shown to resist permeability by HDs are required when administering injectable antineoplastic HDs. For all other activities, the entity's SOP must describe the appropriate PPE to be worn based on its occupational safety plan and assessment of risk (if used). The entity must develop SOPs for PPE based on the risk of exposure (see *Types of Exposure*) and activities performed.

Appropriate PPE must be worn when handling HDs including during:

- Receipt
- Storage
- Transport
- Compounding (sterile and nonsterile)
- Administration
- Deactivation/decontamination, cleaning, and disinfecting
- Spill control
- Waste disposal

7.1 Gloves

When chemotherapy gloves are required, they must meet American Society for Testing and Materials (ASTM) standard D6978 (or its successor). Chemotherapy gloves should be worn for handling all HDs including non-antineoplastics and for reproductive risk only HDs. Chemotherapy gloves must be powder-free because powder can contaminate the work area and can adsorb and retain HDs. Gloves must be inspected for physical defects before use. Do not use gloves with pin holes or weak spots.

When used for sterile compounding, the outer chemotherapy gloves must be sterile. Chemotherapy gloves should be changed every 30 minutes unless otherwise recommended by the manufacturer's documentation and must be changed when torn, punctured, or contaminated. Hands must be washed with soap and water after removing gloves.

7.2 Gowns

When gowns are required, they must be disposable and shown to resist permeability by HDs. Gowns must be selected based on the HDs handled. Disposable gowns made of polyethylene-coated polypropylene or other laminate materials offer better protection than those made of uncoated materials. Gowns must close in the back (i.e., no open front), be long sleeved, and have closed cuffs that are elastic or knit. Gowns must not have seams or closures that could allow HDs to pass through.

Cloth laboratory coats, surgical scrubs, isolation gowns, or other absorbent materials are not appropriate protective outerwear when handling HDs because they permit the permeation of HDs and can hold spilled drugs against the skin, thereby increasing exposure. Clothing may also retain HD residue from contact, and may transfer to other healthcare workers or various surfaces. Washing of non-disposable clothing contaminated with HD residue should only be done according to facility policy as drug residue may be transferred to other clothing. Potentially contaminated clothing must not be taken home under any circumstances.

Gowns must be changed per the manufacturer's information for permeation of the gown. If no permeation information is available for the gowns used, change them every 2–3 hours or immediately after a spill or splash. Gowns worn in HD handling areas must not be worn to other areas in order to avoid spreading HD contamination and exposing other healthcare workers.

7.3 Head, Hair, Shoe, and Sleeve Covers

Head and hair covers (including beard and moustache, if applicable), shoe covers, and sleeve covers provide protection from contact with HD residue. When compounding HDs, a second pair of shoe covers must be donned before entering the C-SEC and doffed when exiting the C-SEC. Shoe covers worn in HD handling areas must not be worn to other areas to avoid spreading HD contamination and exposing other healthcare workers.

Disposable sleeve covers may be used to protect areas of the arm that may come in contact with HDs. Disposable sleeve covers made of polyethylene-coated polypropylene or other laminate materials offer better protection than those made of uncoated materials.

7.4 Eye and Face Protection

Many HDs are irritating to the eyes and mucous membranes. Appropriate eye and face protection must be worn when there is a risk for spills or splashes of HDs or HD waste materials when working outside of a C-PEC (e.g., administration in the surgical suite, working at or above eye level, or cleaning a spill). A full-facepiece respirator provides eye and face protection. Goggles must be used when eye protection is needed. Eye glasses alone or safety glasses with side shields do not protect the eyes adequately from splashes. Face shields in combination with goggles provide a full range of protection against splashes to the face and eyes. Face shields alone do not provide full eye and face protection.

7.5 Respiratory Protection

Personnel who are unpacking HDs that are not contained in plastic should wear an elastomeric half-mask with a multi-gas cartridge and P100-filter until assessment of the packaging integrity can be made to ensure no breakage or spillage occurred during transport. If the type of drug can be better defined, a more targeted cartridge can be used.

Surgical masks do not provide respiratory protection from drug exposure and must not be used when respiratory protection from HD exposure is required. A surgical N95 respirator provides the respiratory protection of an N95 respirator, and like a surgical mask, provides a barrier to splashes, droplets, and sprays around the nose and mouth.

For most activities requiring respiratory protection, a fit-tested NIOSH-certified N95 or more protective respirator is sufficient to protect against airborne particles. However, N95 respirators offer no protection against gases and vapors and little protection against direct liquid splashes (see the Centers for Disease Control and Prevention's (CDC's) Respirator Trusted-Source Information).

Fit test the respirator and train workers to use respiratory protection. Follow all requirements in the Occupational Safety and Health Administration (OSHA) respiratory protection standard (29 CFR 1910.134). An appropriate full-facepiece, chemical cartridge-type respirator or powered air-purifying respirator (PAPR) should be worn when there is a risk of respiratory exposure to HDs, including when:

- Attending to HD spills larger than what can be contained with a spill kit
- Deactivating, decontaminating, and cleaning underneath the work surface of a C-PEC
- There is a known or suspected airborne exposure to powders or vapors

7.6 Disposal of Used Personal Protective Equipment

Consider all PPE worn when handling HDs to be contaminated with, at minimum, trace quantities of HDs. PPE must be placed in an appropriate waste container and further disposed of per local, state, and federal regulations. PPE worn during compounding should be disposed of in the proper waste container before leaving the C-SEC. Chemotherapy gloves and sleeve covers (if used) worn during compounding must be carefully removed and discarded immediately into a waste container approved for trace contaminated waste inside the C-PEC or contained in a sealable bag for discarding outside the C-PEC.

8. HAZARD COMMUNICATION PROGRAM

Entities are required to establish policies and procedures that ensure worker safety during all aspects of HD handling. The entity must develop SOPs to ensure effective training regarding proper labeling, transport, storage, and disposal of the HDs and use of Safety Data Sheets (SDS), based on the Globally Harmonized System of Classification and Labeling of Chemicals (GHS).

Elements of the hazard communication program plan must include:

- A written plan that describes how the standard will be implemented
- All containers of hazardous chemicals must be labeled, tagged, or marked with the identity of the material and appropriate hazard warnings
- Entities must have an SDS for each hazardous chemical they use (29 CFR 1910.1200)
- Entities must ensure that the SDSs for each hazardous chemical used are readily accessible to personnel during each work shift and when they are in their work areas
- Personnel who may be exposed to hazardous chemicals when working must be provided information and training before the initial assignment to work with a hazardous chemical, and also whenever the hazard changes
- Personnel of reproductive capability must confirm in writing that they understand the risks of handling HDs

9. PERSONNEL TRAINING

All personnel who handle HDs must be trained based on their job functions (e.g., in the receipt, storage, compounding, repackaging, dispensing, administrating, and disposing of HDs). Training must occur before the employee independently handles HDs. The effectiveness of training for HD handling competencies must be demonstrated by each employee. Personnel competency must be reassessed at least every 12 months. Personnel must be trained prior to the introduction of a new HD or new equipment and prior to a new or significant change in process or SOP. All training and competency assessment must be documented.

The training must include at least the following:

- Overview of entity's list of HDs and their risks
- Review of the entity's SOPs related to handling of HDs
- Proper use of PPE
- Proper use of equipment and devices (e.g., engineering controls)
- Response to known or suspected HD exposure
- Spill management
- Proper disposal of HDs and trace-contaminated materials

10. RECEIVING

The entity must establish SOPs for receiving HDs. HDs should be received from the supplier in impervious plastic to segregate them from other drugs and to allow for safety in the receiving and internal transfer process. HDs must be delivered to the HD storage area immediately after unpacking.

PPE, including chemotherapy gloves, must be worn when unpacking HDs (see *Personal Protective Equipment*). A spill kit must be accessible in the receiving area.

The entity must enforce policies that include a tiered approach, starting with visual examination of the shipping container for signs of damage or breakage (e.g., visible stains from leakage, sounds of broken glass). *Table 4* summarizes the steps for receiving and handling of damaged shipping containers.

Table 4. Summary of Requirements for Receiving and Handling Damaged HD Shipping Containers

If the shipping container appears damaged	• Seal container without opening and contact the supplier • If the unopened package is to be returned to the supplier, enclose the package in an impervious container and label the outer container "Hazardous" • If the supplier declines return, dispose of as hazardous waste
If a damaged shipping container must be opened	• Seal the container in plastic or an impervious container • Transport it to a C-PEC and place on a plastic-backed preparation mat • Open the package and remove undamaged items • Wipe the outside of the undamaged items with a disposable wipe • Enclose the damaged item(s) in an impervious container and label the outer container "Hazardous" • If the supplier declines return, dispose of as hazardous waste • Deactivate, decontaminate, and clean the C-PEC (see *Deactivating, Decontaminating, Cleaning, and Disinfecting*) and discard the mat and cleaning disposables as hazardous waste

When opening damaged shipping containers, they should preferably be transported to a C-PEC designated for nonsterile compounding. If a C-PEC designated for sterile compounding is the only one available, it must be disinfected after the decontamination, deactivation, and cleaning step before returning to any sterile compounding activity.

Damaged packages or shipping cartons must be considered spills that must be reported to the designated person and managed according to the entity's SOPs. Segregate HDs waiting to be returned to the supplier in a designated negative pressure area. Clean-up must comply with established SOPs.

11. LABELING, PACKAGING, TRANSPORT AND DISPOSAL

The entity must establish SOPs for the labeling, packaging, transport, and disposal of HDs. The SOPs must address prevention of accidental exposures or spills, personnel training on response to exposure, and use of a spill kit. Examples of special exposure-reducing strategies include small-bore connectors (such as Luer Lock) and syringes, syringe caps, CSTDs, the capping of container ports, sealed impervious plastic bags, impact-resistant and/or water-tight containers, and cautionary labeling.

11.1 Labeling

HDs identified by the entity as requiring special HD handling precautions must be clearly labeled at all times during their transport. Personnel must ensure that the labeling processes for compounded preparations do not introduce contamination into the non-HD handling areas.

11.2 Packaging

Personnel must select and use packaging containers and materials that will maintain physical integrity, stability, and sterility (if needed) of the HDs during transport. Packaging materials must protect the HD from damage, leakage, contamination, and degradation, while protecting healthcare workers who transport HDs. The entity must have written SOPs to describe appropriate shipping containers and insulating materials, based on information from product specifications, vendors, and mode of transport.

11.3 Transport

HDs that need to be transported must be labeled, stored, and handled in accordance with applicable federal, state, and local regulations. HDs must be transported in containers that minimize the risk of breakage or leakage. Pneumatic tubes must not be used to transport any liquid HDs or any antineoplastic HDs because of the potential for breakage and contamination.

When shipping HDs to locations outside the entity, the entity must consult the Transport Information on the SDS. The entity must ensure that labels and accessory labeling for the HDs include storage instructions, disposal instructions, and HD category information in a format that is consistent with the carrier's policies.

11.4 Disposal

All personnel who perform routine custodial waste removal and cleaning activities in HD handling areas must be trained in appropriate procedures to protect themselves and the environment to prevent HD contamination. Disposal of all HD waste, including, but not limited to, unused HDs and trace-contaminated PPE and other materials, must comply with all applicable federal, state, and local regulations.

12. DISPENSING FINAL DOSAGE FORMS

HDs that do not require any further manipulation, other than counting or repackaging of final dosage forms, may be prepared for dispensing without any further requirements for containment unless required by the manufacturer or if visual indicators of HD exposure hazards are present (e.g., HD dust or leakage).

Counting or repackaging of HDs must be done carefully. Clean equipment should be dedicated for use with HDs and should be decontaminated after every use. Tablet and capsule forms of antineoplastic HDs must not be placed in automated counting or packaging machines, which subject them to stress and may create powdered contaminants.

13. COMPOUNDING

Entities and personnel involved in compounding HDs must be compliant with the appropriate USP standards for compounding including ⟨795⟩ and ⟨797⟩. Compounding must be done in proper engineering controls as described in *Compounding*. When compounding HD preparations in a C-PEC, a plastic-backed preparation mat should be placed on the work surface of the C-PEC. The mat should be changed immediately if a spill occurs and regularly during use, and should be discarded at the end of the daily compounding activity. Disposable or clean equipment for compounding (such as mortars and pestles, and spatulas) must be dedicated for use with HDs.

Bulk containers of liquid and API HD must be handled carefully to avoid spills. If used, APIs or other powdered HDs must be handled in a C-PEC to protect against occupational exposure, especially during particle-generating activities (such as crushing tablets, opening capsules, and weighing powder).

14. ADMINISTERING

HDs must be administered safely using protective medical devices and techniques. Examples of protective medical devices include needleless and closed systems. Examples of protective techniques include spiking or priming of IV tubing with a non-HD solution in a C-PEC and crushing tablets in a plastic pouch.

Appropriate PPE must be worn when administering HDs. After use, PPE must be removed and disposed of in a waste container approved for trace-contaminated HD waste at the site of drug administration. Equipment (such as tubing and needles) and packaging materials must be disposed of properly, such as in HD waste containers, after administration.

CSTDs must be used for administration of antineoplastic HDs when the dosage form allows. Techniques and ancillary devices that minimize the risk posed by open systems must be used when administering HDs through certain routes. Administration into certain organs or body cavities (e.g., the bladder, eye, peritoneal cavity, or chest cavity) often requires equipment for which locking connections may not be readily available or possible.

Healthcare personnel should avoid manipulating HDs such as crushing tablets or opening capsules if possible. Liquid formulations are preferred if solid oral dosage forms are not appropriate for the patient. If HD dosage forms do require manipulation such as crushing tablet(s) or opening capsule(s) for a single dose, personnel must don appropriate PPE and use a plastic pouch to contain any dust or particles generated.

15. DEACTIVATING, DECONTAMINATING, CLEANING, AND DISINFECTING

All areas where HDs are handled and all reusable equipment and devices must be deactivated, decontaminated, and cleaned. Additionally, sterile compounding areas and devices must be subsequently disinfected.

The entity must establish written procedures for decontamination, deactivation, and cleaning, and for sterile compounding areas disinfection. Additionally, cleaning of nonsterile compounding areas must comply with ⟨795⟩ and cleaning of sterile compounding areas must comply with ⟨797⟩. Written procedures for cleaning must include procedures, agents used, dilutions (if used), frequency, and documentation requirements.

All personnel who perform deactivation, decontamination, cleaning, and disinfection activities in HD handling areas must be trained in appropriate procedures to protect themselves and the environment from contamination. All personnel performing these activities must wear appropriate PPE resistant to the cleaning agents used, including two pairs of chemotherapy gloves and impermeable disposable gowns (see *Personal Protective Equipment*). Additionally, eye protection and face shields must be used if splashing is likely. If warranted by the activity, respiratory protection must be used.

The deactivating, decontaminating, cleaning, and disinfecting agents selected must be appropriate for the type of HD contaminant(s), location, and surface materials. The products used must be compatible with the surface material. Consult manufacturer or supplier information for compatibility with cleaning agents used. Agents used for deactivation, decontamination, and cleaning should be applied through the use of wipes wetted with appropriate solution and not delivered by a spray bottle to avoid spreading HD residue. All disposable materials must be discarded to meet EPA regulations and the entity's policies. Perform cleaning in areas that are sufficiently ventilated. *Table 5* summarizes the purpose and example agents for each step.

Table 5. Cleaning Steps

Cleaning Step	Purpose	Example Agents
Deactivation	Render compound inert or inactive	As listed in the HD labeling or other agents which may incorporate Environmental Protection Agency (EPA)-registered oxidizers (e.g., peroxide formulations, sodium hypochlorite, etc.)
Decontamination	Remove HD residue	Materials that have been validated to be effective for HD decontamination, or through other materials proven to be effective through testing, which may include alcohol, water, peroxide, or sodium hypochlorite
Cleaning	Remove organic and inorganic material	Germicidal detergent

Table 5. Cleaning Steps *(continued)*

Cleaning Step	Purpose	Example Agents
Disinfection (for sterile manipulations)	Destroy microorganisms	EPA-registered disinfectant and/or sterile alcohol as appropriate for use

15.1 Deactivation

Deactivation renders a compound inert or inactive. Residue from deactivation must be removed by decontaminating the surface.

There is no one proven method for deactivating all compounds. The ultimate goal should be complete surface decontamination. Products that have known deactivation properties (EPA-registered oxidizing agents that are appropriate for the intended use) should be used when possible. Care should be taken when selecting materials for deactivation due to potential adverse effects (hazardous byproducts, respiratory effects, and caustic damage to surfaces). Damage to surfaces is exhibited by corrosion to stainless steel surfaces caused by sodium hypochlorite if left untreated. To prevent corrosion, sodium hypochlorite must be neutralized with sodium thiosulfate or by following with an agent to remove the sodium hypochlorite (e.g., sterile alcohol, sterile water, germicidal detergent, or sporicidal agent).

15.2 Decontamination

Decontamination occurs by inactivating, neutralizing, or physically removing HD residue from non-disposable surfaces and transferring it to absorbent, disposable materials (e.g., wipes, pads, or towels) appropriate to the area being cleaned. When choosing among various products available for decontaminating HDs, consideration should be given to surface compatibility and facility requirements. It is imperative to adhere to manufacturer's use instructions. Because of the growing number of assays available for HDs, additional surface wipe sampling is now possible and should be done to document the effectiveness of any agent used for decontamination of HD residue from work surfaces (see *Environmental Quality and Control*).

The amount of HD contamination introduced into the C-PEC may be reduced by wiping down HD containers. The solution used for wiping HD packaging must not alter the product label. The work surface of the C-PEC must be decontaminated between compounding of different HDs. The C-PEC must be decontaminated at least daily (when used), any time a spill occurs, before and after certification, any time voluntary interruption occurs, and if the ventilation tool is moved.

C-PECs may have areas under the work tray where contamination can build up. These areas must be deactivated, decontaminated, and cleaned at least monthly to reduce the contamination level in the C-PEC. Accessing this area may be difficult. Deactivate, decontaminate, and clean as much as possible of the C-PEC surfaces before accessing the area under the work tray. When deactivating, decontaminating, and cleaning the area under the work tray of a C-PEC, the containment airflows are compromised by opening the cabinets. To provide protection to the worker performing this task, respiratory protection may be required.

15.3 Cleaning

Cleaning is a process that results in the removal of contaminants (e.g., soil, microbial contamination, HD residue) from objects and surfaces using water, detergents, surfactants, solvents, and/or other chemicals. Cleaning agents used on compounding equipment should not introduce microbial contamination. No cleaning step may be performed when compounding activities are occurring.

15.4 Disinfection

Disinfection is a process of inhibiting or destroying microorganisms. Before disinfection can be adequately performed, surfaces must be cleaned. Disinfection must be done for areas intended to be sterile, including the sterile compounding areas.

16. SPILL CONTROL

All personnel who may be required to clean up a spill of HDs must receive proper training in spill management and the use of PPE and NIOSH-certified respirators (see *Personal Protective Equipment*). Spills must be contained and cleaned immediately only by qualified personnel with appropriate PPE. Qualified personnel must be available at all times while HDs are being handled. Signs must be available for restricting access to the spill area. Spill kits containing all of the materials needed to clean HD spills must be readily available in all areas where HDs are routinely handled. If HDs are being prepared or administered in a non-routine healthcare area, a spill kit and respirator must be available. All spill materials must be disposed of as hazardous waste.

The circumstances and management of spills must be documented. Personnel who are potentially exposed during the spill or spill clean up or who have direct skin or eye contact with HDs require immediate evaluation. Non-employees exposed to an HD spill should follow entity policy, which may include reporting to the designated emergency service for initial evaluation and completion of an incident report or exposure form.

SOPs must be developed to prevent spills and to direct the clean up of HD spills. SOPs must address the size and scope of the spill and specify who is responsible for spill management and the type of PPE required. The management of the spill (e.g., decontamination, deactivation, and cleaning) may be dependent on the size and type of spill. The SOP must address the location of spill kits and clean-up materials as well as the capacity of the spill kit. Written procedures should address use of appropriate full-facepiece, chemical cartridge-type respirators if the capacity of the spill kit is exceeded or if there is known or suspected airborne exposure to vapors or gases.

17. DOCUMENTATION AND STANDARD OPERATING PROCEDURES

The entity must maintain SOPs for the safe handling of HDs for all situations in which these HDs are used throughout a facility. The SOPs must be reviewed at least every 12 months by the designated person, and the review must be documented. Revisions in forms or records must be made as needed and communicated to all personnel handling HDs.

The SOPs for handling of HDs should include:

- Hazard communication program
- Occupational safety program
- Designation of HD areas
- Receipt
- Storage
- Compounding
- Use and maintenance of proper engineering controls (e.g., C-PECs, C-SECs, and CSTDs)
- Hand hygiene and use of PPE based on activity (e.g., receipt, transport, compounding, administration, spill, and disposal)
- Deactivation, decontamination, cleaning, and disinfection
- Dispensing
- Transport
- Administering
- Environmental monitoring (e.g., wipe sampling)
- Disposal
- Spill control
- Medical surveillance

Personnel who transport, compound, or administer HDs must document their training according to OSHA standards (see OSHA Standard 1910.120 Hazardous Waste Operations and Emergency Response) and other applicable laws and regulations.

18. MEDICAL SURVEILLANCE

Medical surveillance is part of a comprehensive exposure control program complementing engineering controls, safe work processes, and use of PPE. Healthcare workers who handle HDs as a regular part of their job assignment should be enrolled in a medical surveillance program. The general purpose of surveillance is to minimize adverse health effects in personnel potentially exposed to HDs. Medical surveillance programs involve assessment and documentation of symptom complaints, physical findings, and laboratory values (such as a blood count) to determine whether there is a deviation from the expected norms.

Medical surveillance can also be viewed as a secondary prevention tool that may provide a means of early detection if a health problem develops. Tracking personnel through medical surveillance allows the comparison of health variables over time in individual workers, which may facilitate early detection of a change in a laboratory value or health condition. Medical surveillance programs also look for trends in populations of workers. Examining grouped data compared with data from unexposed workers may reveal a small alteration or increase in the frequency of a health effect that would be obscured if individual workers' results alone were considered.

Medical surveillance evaluates the protection afforded by engineering controls, other administrative controls, safe work processes, PPE, and worker education about the hazards of the materials they work with in the course of their duties. The data-gathering elements of a medical surveillance program are used to establish a baseline of workers' health and then to monitor their future health for any changes that may result from exposure to HDs.

Elements of a medical surveillance program should be consistent with the entity's Human Resource policies and should include:

- Development of an organized approach to identify workers who are potentially exposed to HDs on the basis of their job duties
- Use of an entity-based or contracted employee health service to perform the medical surveillance while protecting the confidentiality of the employees' personal medical information
- Initial baseline assessment (pre-placement) of a worker's health status and medical history. Data elements collected include a medical (including reproductive) history and work history to assess exposure to HDs, physical examination, and laboratory testing. Methods used to assess exposure history include a review of:
    - Records of HDs handled, with quantities and dosage forms
    - Estimated number of HDs handled per week
    - Estimates of hours spent handling HDs per week and/or per month
    - Performance of a physical assessment and laboratory studies linked to target organs of commonly used HDs, such as a baseline complete blood count. Biological monitoring to determine blood or urine levels of specific HDs is not currently recommended in surveillance protocols, but may have a role in the follow-up of acute spills with a specific agent.
- Medical records of surveillance should be maintained according to OSHA regulation concerning access to employee exposure and medical records
- Monitoring workers' health prospectively through periodic surveillance using the elements of data gathering described above (updated health and exposure history, physical assessment, and laboratory measures, if appropriate)

- Monitoring of the data to identify prevention failure leading to health effects; this monitoring may occur in collaboration with the employee health service
- Development of a follow-up plan for workers who have shown health changes suggesting toxicity or who have experienced an acute exposure. This follow-up should include evaluation of current engineering and administrative controls and equipment to ensure that all systems are appropriately and accurately implemented (see *Follow-Up Plan*)
- Completion of an exit examination when a worker's employment at the entity ends, to document the information on the employee's medical, reproductive, and exposure histories. Examination and laboratory evaluation should be guided by the individual's history of exposures and follow the outline of the periodic evaluation

18.1 Follow-Up Plan

The occurrence of exposure-related health changes should prompt immediate re-evaluation of primary preventive measures (e.g., administrative and engineering controls, PPE, and others). In this manner, medical surveillance acts as a check on the effectiveness of controls already in use.

The entity should take the following actions:

- Perform a post-exposure examination tailored to the type of exposure (e.g., spills or needle sticks from syringes containing HDs). An assessment of the extent of exposure should be conducted and included in a confidential database and in an incident report. The physical examination should focus on the involved area as well as other organ systems commonly affected (i.e., the skin and mucous membranes for direct contact or inhalation; the pulmonary system for aerosolized HDs). Treatment and laboratory studies will follow as indicated and be guided by emergency protocols
- Compare performance of controls with recommended standards; conduct environmental sampling when analytical methods are available
- Verify and document that all engineering controls are in proper operating condition
- Verify and document that the worker complied with existing policies. Review policies for the use of PPE and employee compliance with PPE use and policies. Review availability of appropriate PPE (see *Personal Protective Equipment*)
- Develop and document a plan of action that will prevent additional exposure of workers
- Ensure confidential, two-way communication between the worker and the employee health unit(s) regarding notification, discussions about a change in health condition, or detection of an adverse health effect
- Provide and document a follow-up medical survey to demonstrate that the plan implemented is effective
- Ensure that any exposed worker receives confidential notification of any adverse health effect. Offer alternative duty or temporary reassignment
- Provide ongoing medical surveillance of all workers at risk for exposure to HDs to determine whether the plan implemented is effective

GLOSSARY

Active pharmaceutical ingredient (API): Any substance or mixture of substances intended to be used in the compounding of a drug preparation, thereby becoming the active ingredient in that preparation and furnishing pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease in humans and animals or affecting the structure and function of the body.

Alternative duty: Performance of other tasks that do not include the direct handling of HDs.

Ante-room: An ISO Class 7 or cleaner room where personnel hand hygiene, garbing procedures, and other activities that generate high particulate levels are performed. The ante-room is the transition room between the unclassified area of the facility and the buffer room.

Assessment of risk: Evaluation of risk to determine alternative containment strategies and/or work practices.

Beyond-use date (BUD): The date or time beyond which a compounded preparation cannot not be used and must be discarded (see ⟨795⟩ and ⟨797⟩). The date or time is determined from the date or time when the preparation was compounded.

Biological safety cabinet (BSC): A ventilated cabinet often used for preparation of hazardous drugs. These cabinets are divided into three general classes (Class I, Class II, and Class III). Class II BSCs are further divided into types (Type A1, Type A2, Type B1, and Type B2). See *Appendix 3* for details.

Buffer room: A type of C-SEC under negative pressure that meets ISO Class 7 or better air quality where the C-PEC that generates and maintains an ISO Class 5 environment is physically located. Activities that occur in this area are limited to the preparation and staging of components and supplies used when compounding HDs.

Chemotherapy glove: A medical glove that meets the ASTM Standard Practice for Assessment of Resistance of Medical Gloves to Permeation by Chemotherapy Drugs (D6978) or its successor.

Classified space: An area that maintains an air cleanliness classification based on the International Organization for Standardization (ISO).

Cleaning: The process of removing soil (e.g., organic and inorganic material) from objects and surfaces, normally accomplished by manually or mechanically using water with detergents or enzymatic products.

Closed-system drug-transfer device (CSTD): A drug-transfer device that mechanically prohibits the transfer of environmental contaminants into the system and the escape of HD or vapor concentrations outside the system.

Compounded preparation: A nonsterile or sterile drug or nutrient preparation that is compounded in a licensed pharmacy or other healthcare-related facility in response to or anticipation of a prescription or a medication order from a licensed prescriber.

Compounding aseptic containment isolator (CACI): A specific type of CAI that is designed for the compounding of sterile HDs. The CACI is designed to provide worker protection from exposure to undesirable levels of airborne drugs throughout the compounding and material transfer processes and to provide an aseptic environment with unidirectional airflow for compounding sterile preparations.

Compounding aseptic isolator (CAI): An isolator specifically designed for compounding sterile, non-hazardous pharmaceutical ingredients or preparations. The CAI is designed to maintain an aseptic compounding environment throughout the compounding and material transfer processes.

Compounding personnel: Individuals who participate in the compounding process.

Containment primary engineering control (C-PEC): A ventilated device designed and operated to minimize worker and environmental exposures to HDs by controlling emissions of airborne contaminants through the following:

- The full or partial enclosure of a potential contaminant source
- The use of airflow capture velocities to trap and remove airborne contaminants near their point of generation
- The use of air pressure relationships that define the direction of airflow into the cabinet
- The use of HEPA filtration on all potentially contaminated exhaust streams

Containment secondary engineering control (C-SEC): The room with fixed walls in which the C-PEC is placed. It incorporates specific design and operational parameters required to contain the potential hazard within the compounding room.

Containment segregated compounding area (C-SCA): A type of C-SEC with nominal requirements for airflow and room pressurization as they pertain to HD compounding.

Containment ventilated enclosure (CVE): A full or partial enclosure that uses ventilation principles to capture, contain, and remove airborne contaminants through HEPA filtration and prevent their release into the work environment.

Deactivation: Treatment of an HD contaminant on surfaces with a chemical, heat, ultraviolet light, or another agent to transform the HD into a less hazardous agent.

Decontamination: Inactivation, neutralization, or removal of HD contaminants on surfaces, usually by chemical means.

Doff: To remove PPE.

Don: To put on PPE.

Disinfection: The process of inhibiting or destroying microorganisms.

Engineering control: Primary, secondary, and supplemental devices designed to eliminate or reduce worker exposure to HDs.

EPA-registered disinfectant: Antimicrobial products registered with the Environmental Protection Agency (EPA) for healthcare use against pathogens specified in the product labeling.

Externally vented: Exhausted to the outside.

Final dosage form: Any form of a medication that requires no further manipulation before administration.

Globally Harmonized System of Classification and Labeling of Chemicals (GHS): A system for standardizing and harmonizing the classification and labeling of chemicals.

Goggles: Tight-fitting eye protection that completely covers the eyes, eye sockets, and facial area that immediately surrounds the eyes. Goggles provide protection from impact, dust, and splashes. Some goggles fit over corrective lenses.

Hazardous drug (HD): Any drug identified by at least one of the following criteria:

- Carcinogenicity, teratogenicity, or developmental toxicity
- Reproductive toxicity in humans
- Organ toxicity at low dose in humans or animals
- Genotoxicity or new drugs that mimic existing HDs in structure or toxicity

High-efficiency particulate air (HEPA) filtration: An extended-medium, dry-type filter in a rigid frame, having a minimum particle collection efficiency of 99.97% for particles with a mass median diameter of 0.3 µm when tested at a rated airflow in accordance with MIL STD 282 using IEST Recommended Standard RP-CC001.5.

Negative-pressure room: A room that is maintained at a lower pressure than the adjacent areas; therefore the net flow of air is into the room.

Pass-through: An enclosure with interlocking doors that is positioned between two spaces for the purpose of reducing particulate transfer while moving materials from one space to another. A pass-through serving negative-pressure rooms needs to be equipped with sealed doors.

Personal protective equipment (PPE): Items such as gloves, gowns, respirators, goggles, faceshields, and others that protect individual workers from hazardous physical or chemical exposures.

Positive-pressure room: A room that is maintained at a higher pressure than the adjacent areas; therefore, the net flow of air is out of the room.

Repackaging: The act of removing a product from its original primary container and placing it into another primary container, usually of smaller size.

Safety data sheet (SDS): An informational document that provides written or printed material concerning a hazardous chemical. The SDS is prepared in accordance with the HCS [previously known as a Material Safety Data Sheet (MSDS)].

Spill kit: A container of supplies, warning signage, and related materials used to contain the spill of an HD.

Standard operating procedure (SOP): Written procedures describing operations, testing, sampling, interpretation of results, and corrective actions that relate to the operations that are taking place.

Supplemental engineering control: An adjunct control (e.g., CSTD) that may be used concurrently with primary and secondary engineering controls. Supplemental engineering controls offer additional levels of protection and may facilitate enhanced occupational protection, especially when handling HDs outside of primary and secondary engineering controls (e.g., during administering).

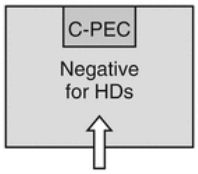
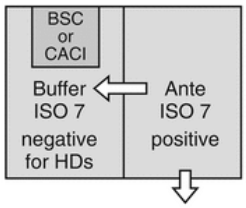
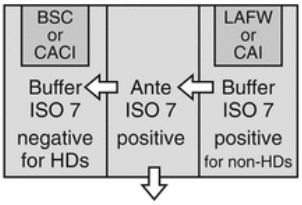
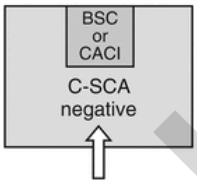
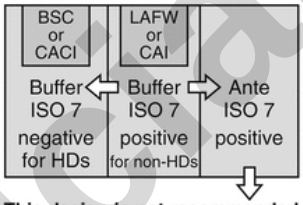
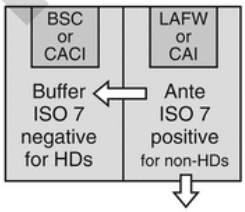
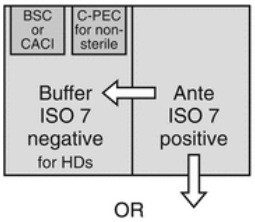
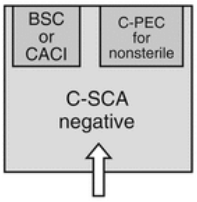
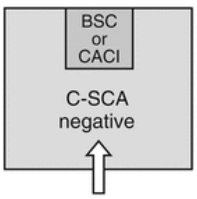
Unclassified space: A space not required to meet any air cleanliness classification based on the International Organization for Standardization (ISO).

APPENDICES

Appendix 1: Acronyms

ACPH	Air changes per hour
API	Active pharmaceutical ingredient
ASTM	American Society for Testing and Materials
BSC	Biological safety cabinet
BUD	Beyond-use date
CACI	Compounding aseptic containment isolator
CAI	Compounding aseptic isolator
CDC	Centers for Disease Control and Prevention
C-PEC	Containment primary engineering control
C-SCA	Containment segregated compounding area
C-SEC	Containment secondary engineering control
CSP	Compounded sterile preparation
CSTD	Closed-system drug-transfer device
CVE	Containment ventilated enclosure
EPA	Environmental Protection Agency
GHS	Globally Harmonized System of Classification and Labeling of Chemicals
HCS	Hazard Communication Standard
HD	Hazardous drug
HEPA	High-efficiency particulate air
IV	Intravenous
LAFW	Laminar airflow workbench
NIOSH	National Institute for Occupational Safety and Health
ONS	Oncology Nursing Society
OSHA	Occupational Safety and Health Administration
PAPR	Powered air-purified respirator
PPE	Personal protective equipment
SDS	Safety Data Sheet
SOP	Standard operating procedure
ULPA	Ultra-low particulate air
UPS	Uninterrupted power source

Appendix 2: Examples of Designs for Hazardous Drug Compounding Areas[a]

Use	Optimal Primary and Secondary Control	Minimum ACPH	Limitations Primary and Secondary Control	Minimum ACPH	Notes for limitations
Nonsterile HD compounding		12			
Sterile HD compounding	 OR 	30	 OR  **This design is not recommended** OR  Typically used in oncology clinic settings.	12 30 30	Maximum BUD as described in <797> for segregated compounding area. If this design is in place, measures must be taken to avoid contamination of the positive-pressure buffer room. Maximum BUD as described in <797>.
Both sterile HD and nonsterile HD compounding	A separate room for sterile and nonsterile compounding is recommended		 OR  OR 	30 12 12	For rooms used for both sterile and nonsterile compounding, particle-generating activity must not be performed when sterile compounding is in process. C-PECs must be at least 1 meter apart. Maximum BUD as described in <797> for segregated compounding area. Maximum BUD as described in <797> for segregated compounding area.

[a] The arrows indicate direction of airflow.

Appendix 3: Types of Biological Safety Cabinets

Class I: A BSC that protects personnel and the environment but does not protect the product/preparation. A minimum velocity of 75 linear feet/minute of unfiltered room air is drawn through the front opening and across the work surface, providing personnel protection. The air is then passed through a HEPA/ULPA (ultra-low particulate air) filter, either into the room or to the outside in the exhaust plenum, providing environmental protection.

Class II: Class II (Types A1, A2, B1, and B2) BSCs are partial barrier systems that rely on the movement of air to provide personnel, environmental, and product/preparation protection. Personnel and product/preparation protection are provided by the combination of inward and downward airflow captured by the front grille of the cabinet. Side-to-side cross-contamination of products/preparations is minimized by the internal downward flow of HEPA/ULPA filtered air moving toward the work surface and then drawn into the front and rear intake grilles. Environmental protection is provided when the cabinet exhaust air is passed through a HEPA/ULPA filter.

Type A1 (formerly, Type A): These Class II BSCs maintain a minimum inflow velocity of 75 feet/minute; have HEPA-filtered, down-flow air that is a portion of the mixed down-flow and inflow air from a common plenum; may exhaust HEPA-filtered air back into the laboratory or to the environment through an exhaust canopy; and may have positive-pressure contaminated ducts and plenums that are not surrounded by negative-pressure plenums. Type A1 BSCs are not suitable for use with volatile toxic chemicals and volatile radionuclides.

Type A2 (formerly, Type B3): These Class II BSCs maintain a minimum inflow velocity of 100 feet/minute; have HEPA-filtered, down-flow air that is a portion of the mixed down-flow and inflow air from a common exhaust plenum; may exhaust HEPA-filtered air back into the laboratory or to the environment through an exhaust canopy; and have all contaminated ducts and plenums under negative pressure or surrounded by negative-pressure ducts and plenums. If these cabinets are used for minute quantities of volatile toxic chemicals and trace amounts of radionuclides, they must be exhausted through properly functioning exhaust canopies.

Type B1: These Class II BSCs maintain a minimum inflow velocity of 100 feet/minute; have HEPA-filtered, down-flow air composed largely of uncontaminated, recirculated inflow air; exhaust most of the contaminated down-flow air through a dedicated duct exhausted to the atmosphere after passing it through a HEPA filter; and have all contaminated ducts and plenums under negative pressure or surrounded by negative-pressure ducts and plenums. If these cabinets are used for work involving minute quantities of volatile toxic chemicals and trace amounts of radionuclides, the work must be done in the directly exhausted portion of the cabinet.

Type B2 (total exhaust): These Class II BSCs maintain a minimum inflow velocity of 100 feet/minute; have HEPA-filtered, down-flow air drawn from the laboratory or the outside; exhaust all inflow and down-flow air to the atmosphere after filtration through a HEPA filter without recirculation inside the cabinet or return to the laboratory; and have all contaminated ducts and plenums under negative pressure or surrounded by directly exhausted negative-pressure ducts and plenums. These cabinets may be used with volatile toxic chemicals and radionuclides.

Class III: The Class III BSC is designed for work with highly infectious microbiological agents and other hazardous operations. It provides maximum protection for the environment and the worker. It is a gas-tight enclosure with a viewing window that is secured with locks and/or requires the use of tools to open. Both supply and exhaust air are HEPA/ULPA filtered. Exhaust air must pass through two HEPA/ULPA filters in series before discharge to the outdoors.

REFERENCES

1. American College of Occupational and Environmental Medicine: ACOEM Task Force on Reproductive Toxicology. Reproductive and developmental hazard management guidance. April 26, 2011.
2. American Society of Clinical Oncology. Worker safety when handling hazardous drugs is focus of statement by oncology societies. March 3, 2015.
3. American Society of Health-System Pharmacists. ASHP guidelines on compounding sterile preparations. *Am J Health-Syst Pharm.* 2014;71(2):145–166.
4. American Society of Health-System Pharmacists. ASHP guidelines on handling hazardous drugs. *Am J Health-Syst Pharm.* 2006; 63:1172–1193.
5. Baker EL, editor. Surveillance in occupational health and safety. *Am J Public Health.* 1989;*79*(Suppl.):1–63.
6. Chaffee BW, Armitstead JA, Benjamin BE, Cotugno MC, Forrey RA, Hintzen BL, et al. Guidelines for the safe handling of hazardous drugs: consensus recommendations. *Am J Health-Syst Pharm.* 2010;67(18):1545–1546.
7. Connor TH. Permeability of nitrile rubber, latex, polyurethane, and neoprene gloves to 18 antineoplastic drugs. *Am J Health-Syst Pharm.* 1999;56(23):2450–2453.
8. Connor TH, Mackenzie BA, DeBord DG. Clarification about hazardous drugs. *Am J Health-Syst Pharm.* 2012;*69*(22):1949–1950.
9. Controlled Environment Testing Association. CETA application guide for informational notes to meet the NSF/ANSI 49:2010a standard requirements CAG-010-2011. July 1, 2011. Raleigh, NC: CETA; 2011.
10. Controlled Environment Testing Association. CETA application guide for the use of surface decontaminants in biosafety cabinets CAG-004-2007. January 30, 2007. Raleigh, NC:ETA;2007.
11. Controlled Environment Testing Association. CETA compounding isolator testing guide, CAG-002-2006. Revised December 8, 2008.Raleigh, NC: CETA; 2008.
12. Controlled Environment Testing Association. CETA CAG-005-2007 servicing hazardous drug compounding primary engineering controls. Raleigh, NC: CETA; 2007.

13. Centers for Disease Control and Prevention. Biosafety in microbiological and biomedical laboratories (BMBL) 5th edition. Page last updated: March 13, 2015. Atlanta, GA: CDC, 2015. http://www.cdc.gov/biosafety/publications/bmbl5.
14. Centers for Disease Control and Prevention. Workplace safety and health: *Chemotherapy drug exposures at an oncology clinic—Florida.* June 2012. Atlanta, GA: CDC; 2012 http://www.cdc.gov/niosh/hhe/reports/pdfs/2009-0148-3158.pdf.
15. Centers for Disease Control and Prevention. Hand hygiene in healthcare settings. Page last updated: May 1, 2015. Atlanta, GA: CDC; 2015. http://www.cdc.gov/handhygiene/.
16. Centers for Disease Control and Prevention. NIOSH Alert: preventing occupational exposures to antineoplastic and other hazardous drugs in health care settings Cincinnati, OH: Department of Health and Human Services, CDC; 2004.
17. NIOSH list of antineoplastic and other hazardous drugs in healthcare settings, 2014 Cincinnati, OH: Department of Health and Human Services, CDC; 2014.
18. Centers for Disease Control and Prevention. The National Personal Protective Technology Laboratory (NPPTL). Respirator trusted-source information. Section 3: ancillary respirator information. Atlanta, GA: CDC; 2014. http://www.cdc.gov/niosh/npptl/topics/respirators/disp_part/respsource3.html.
19. Centers for Disease Control and Prevention. Workplace solutions: medical surveillance for healthcare workers exposed to hazardous drugs. Department of Health and Human Services, CDC; 2012.
20. Centers for Disease Control and Prevention. Workplace solutions: personal protective equipment for health care workers who work with hazardous drugs. Cincinnati, OH: Department of Health and Human Services, CDC; 2009.
21. Centers for Disease Control and Prevention. Workplace solutions: safe handling of hazardous drugs for veterinary healthcare workers. Cincinnati, OH: Department of Health and Human Services, CDC; 2010.
22. Goodin S, Griffith N, Chen B, Chuk K, Daouphars M, Doreau C, et al. Safe handling of oral chemotherapeutic agents in clinical practice: recommendations from an international pharmacy panel. *J Oncol Pract.* 2011;7(1):7–12.
23. Hematology/Oncology Pharmacy Association. Ensuring healthcare worker safety when handling hazardous drugs: the joint position statement from the Oncology Nursing Society, the American Society of Clinical Oncology, and the Hematology/Oncology Pharmacy Association. 2015. http://www.hoparx.org/uploads/HOPA_ASCO_ONS_Joint_Position.pdf
24. International Society of Oncology Pharmacy Practitioners Standards Committee. ISOPP standards of practice. Safe handling of cytotoxics. *J Oncol Pharm Pract.* 2007;13 Suppl:1–81.
25. Massoomi F. The evolution of the CSTD. *Oncology Safety* 2015;12(2 suppl).
26. McDiarmid MA, Emmett EA. Biological monitoring and medical surveillance of workers exposed to antineoplastic agents. *Semin Occup Med.* 1987;2(2):109–117.
27. NST International. NSF/ANSI 49-2011. Biosafety cabinetry: design, construction, performance, and field certification. Annex E. 2011.
28. Neuss MN, Polovich M, McNiff K, Esper P, Gilmore TR, LeFebvre KB, et al. 2013 updated American Society of Clinical Oncology/Oncology Nursing Society chemotherapy administration safety standards including standards for the safe administration and management of oral chemotherapy, *Oncol Nursing Forum.* 2013;40(3):225–233.
29. Oncology Nursing Society. Safe handling of hazardous drugs. In: Polovich M, editor. 2nd ed. Pittsburgh, PA: *Oncology Nursing Society;* 2011.
30. Oncology Nursing Society, American Society of Clinical Oncology, and Hematology/Oncology Pharmacy Association. Joint position statement: ensuring healthcare worker safety when handling hazardous drugs. 2015. https://www.ons.org/advocacy-policy/positions/practice/hazardous-drugs
31. Occupational Safety and Health Administration, The Joint Commission, and NIOSH letter to hospitals, April 4, 2011. Washington, DC: United States Department of Labor. http://www.osha.gov/ooc/drug-letter.pdf.
32. Occupational Safety and Health Administration. Hospital respiratory protection program toolkit. OSHA publication number 3767-05 2015.
33. Occupational Safety and Health Administration. Occupational Safety and Health Standards: hazard communication. Washington, DC: United States Department of Labor; 2012. http://www.osha.gov/dsg/hazcom/standards.html.
34. Occupational Safety and Health Administration. Occupational Safety and Health Standards: access to employee exposure and medical records [29 CFR 1910.1020]. Washington, DC: United States Department of Labor.
35. Occupational Safety and Health Administration. Occupational Safety and Health Standards: hazardous waste operations and emergency response [29 CFR 1910.120]. Washington, DC: United States Department of Labor.
36. OSHA Technical Manual Controlling occupational exposure to hazardous drugs. Section VI, Chapter 2. Washington, DC: United States Department of Labor;1999.
37. Occupational Safety and Health Administration. Personal protective equipment. Washington, DC: United States Department of Labor; 2003.
38. Occupational Safety and Health Administration. *Respiratory protection eTool* [29 CFR 1910.134]. Washington, DC: United States Department of Labor.
39. Occupational Safety and Health Administration. Occupational Safety and Health Standards: toxic and hazardous substances [CFR 1910.1200]. Washington, DC: United States Department of Labor; 2013. https://www.osha.gov/SLTC/hazardoustoxicsubstances/index.html
40. Power LA. Closed-system transfer devices for safe handling of injectable hazardous drugs. *Pharm Pract News*. New York: McMahon Publishing Group; June 2013;1-16.
41. Power LA, Sessink PJM, Gesy K, Charbonneau F. Hazardous drug residue on exterior vial surfaces: evaluation of a commercial manufacturing process. *Hosp Pharm.* 2014;49(4):355–362.
42. Sessink PJM, Trahan J, Coyne JW. Reduction in surface contamination with cyclophosphamide in 30 US hospital pharmacies following implementation of a closed-system drug transfer device. *Hosp Pharm.* 2013;48(3):204–212.

43. University HealthSystem Consortium. UHC consensus statement: model hazardous drug safety plan for institutions. Chicago, IL: UHC; October 2009, revised January 2011.
44. Watts D. Gloves as PPE: standards for permeation and penetration. *Clean Air Containment Rev*. Issue 2;April 2010:16-20.
45. Wesdock JC, Sokas RK. Medical surveillance in work-site safety and health programs. *Am Fam Physician.* 2000;61(9):2785–2790.

Change to read:

⟨825⟩ RADIOPHARMACEUTICALS—PREPARATION, COMPOUNDING, DISPENSING, AND REPACKAGING

▲**The official date for this chapter is December 1, 2020.** USP General Chapter ⟨825⟩ is informational and not compendially applicable unless otherwise specified by regulators and enforcement bodies. For information on the scope, intended applicability, and implementation context for USP General Chapter ⟨825⟩, see Role and Applicability of USP General Chapter ⟨825⟩ Related to Radiopharmaceuticals.▲ (RB 1-Dec-2020)

1. INTRODUCTION

Radiopharmaceuticals, as defined in this chapter (see *Glossary*), are a subset of radioactive materials (RAMs) falling under the control of the US Nuclear Regulatory Commission (NRC) or NRC-contracted agreement state agency. Radiopharmaceuticals are also a subset of prescription drugs falling under the control of the US FDA for manufacturing and marketing. Other federal regulatory authorities (e.g., Department of Transportation) have control over certain activities related to radiopharmaceuticals. Compliance with these regulations, as applicable, must be ensured in addition to compliance with the standards described in this chapter. [NOTE—Users outside the US must comply with equivalent regulations, as applicable, pertaining to radiopharmaceuticals.]

This chapter is intended to provide uniform minimum standards for the preparation, compounding, dispensing, and repackaging of sterile and nonsterile radiopharmaceuticals for humans and animals that occur as part of state-licensed activities (e.g., the practice of pharmacy and the practice of medicine). These standards apply to all radiopharmaceutical processing activities, including those with radionuclides that emit a single photon, a positron, or a therapeutic particle. Furthermore, these standards apply to sterile intravascular radioactive devices (e.g., radioactive microspheres for intravascular brachytherapy).

This chapter does not apply to the following activities:

- Manufacturing of approved radiopharmaceuticals (e.g., NDA, ANDA, BLA) in FDA-registered manufacturing establishments
- Manufacturing of radiopharmaceuticals as investigational agents (e.g., IND, RDRC)
- Compounding of radiopharmaceuticals in a registered FDCA §503B outsourcing facility
- Preparation/compounding of positron emission tomography (PET) drugs that are not manufactured as approved drug products (e.g., NDA, ANDA, BLA) and conforms with *Positron Emission Tomography Drugs for Compounding, Investigational, and Research Uses* ⟨823⟩
- Administration of radiopharmaceuticals to patients

In each of these scenarios except for patient administration, the further processing and manipulation of the drug product after release falls within the scope of this chapter.

This chapter does not apply to the preparation of non-radioactive drugs, including those used as pharmacologic adjuncts for certain nuclear medicine procedures. These drugs must be prepared following standards described in *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩ and *Pharmaceutical Compounding—Sterile Preparations* ⟨797⟩.

This chapter applies to all practice settings where radiopharmaceuticals are prepared, compounded, dispensed, or repackaged. Practice settings consist of state-licensed nuclear pharmacies, federal nuclear pharmacy facilities, and other healthcare facilities, including, but not limited to: nuclear medicine departments in hospitals and clinics, nuclear cardiology clinics (fixed site or mobile), and other specialty clinics.

This chapter applies to all individuals who prepare, compound, dispense, or repackage radiopharmaceuticals. Applicable individuals consist of authorized nuclear pharmacists (ANPs) and authorized user (AU) physicians, as well as individuals working under their supervision. This includes, but is not limited to, student pharmacists, nuclear pharmacy technicians, nuclear medicine technologists and students, and physician residents and trainees.

US federal and state radiation regulatory authorities require limiting radiation exposure to personnel who handle radiopharmaceuticals, which necessitates special provisions for radiation protection. The principles of radiation safety involve time, distance, shielding, and radioactive contamination control. Moreover, the use of radiation detection and measuring devices is a necessary component of radiopharmaceutical handling procedures. Strict adherence to all typical aseptic handling practices is not possible in many scenarios where radiopharmaceuticals are handled. Thus, it is necessary to balance aseptic handling practices (patient safety) with radiation protection practices (worker safety). This chapter describes appropriate strategies that provide assurance of maintaining patient safety, while also ensuring the safety of individuals performing these activities. Because radiopharmaceuticals represent a unique class of prescription drugs, the use of technologies, techniques, materials, and procedures other than those described in this chapter are not prohibited so long as they are documented to be equivalent or superior to those described herein.

1.1 Nonsterile Radiopharmaceuticals

Examples of nonsterile radiopharmaceuticals include oral capsules and oral solutions. For conventionally manufactured products or compounded preparations obtained from 503B-registered outsourcing facilities, dispensing can proceed as described in *12. Dispensing*. For prepared or compounded preparations, such preparations must comply with applicable identity, quality, and purity standards, as described in manufacturer labeling, *USP* monographs, or other appropriate sources (e.g., documented, peer-reviewed materials). They can then be dispensed as described in this chapter.

1.2 Sterile Radiopharmaceuticals

Examples of sterile radiopharmaceuticals include injectables (e.g., intravenous, intrathecal, intraperitoneal, subcutaneous, and intradermal), inhalations, ophthalmics, and intra-organ instillations. For conventionally marketed products, see *12. Dispensing*. For prepared or compounded preparations, such preparations must comply with applicable identity, quality, and purity standards. For compounded preparations involving one or more nonsterile components, a sterilization procedure (e.g., filtration with bubble point testing) must be performed prior to dispensing. For injectable compounded preparations involving one or more components that are not certified to be pyrogen-free, bacterial endotoxin testing, as defined in *Bacterial Endotoxins Test* ⟨85⟩, must be performed prior to dispensing.

The most important factor for maintaining sterility is the avoidance of touch contamination. Wipe the vial septum with sterile 70% isopropyl alcohol (IPA) prior to initial needle puncture. If the vial shield top is then closed, the septum must be disinfected again with sterile 70% IPA prior to another needle puncture. Some vial shields are constructed such that the vial septum is recessed and difficult to access. One approach for disinfecting the vial septum in this type of vial shield is to use right-angle forceps to hold a sterile 70% IPA wipe and apply direct contact with the vial septum. It is also acknowledged that such vial shields disrupt first air contacting the vial septum during certain handling conditions. Wipe the septum with sterile 70% IPA frequently whenever multiple punctures are occurring (e.g., removing several individual doses from a multiple-dose container).

2. RADIATION SAFETY CONSIDERATIONS

The handling of radiopharmaceuticals necessitates meeting the radiation regulatory agency requirements for worker safety. This involves licensing commitments to keep all exposure levels for the workers involved as low as reasonably achievable (ALARA) practices. Principles of radiation safety involve time, distance, shielding, and contamination control. Moreover, radiation detection and measuring devices are necessary. Aseptic handling practices must be balanced with radiation safety considerations, based on the following:

- Knowledge, training, experience, and professional judgment related to the type, abundance, and energy of the radioactive emissions
- The quantity of radioactivity, volume, handling steps, and timing
- Other factors, which can vary on a case-by-case basis

2.1 Time

Radiation exposure to personnel is directly proportional to the quantity of radiation handled and the time handling the RAM; minimizing handling time will minimize radiation exposure. Personnel handling radiopharmaceuticals may work quickly in a controlled and safe manner, including multiple hand movements in and out of the ISO Class 5 primary engineering control (PEC) during aseptic processes.

2.2 Distance

Radiation exposure follows the inverse square law; increasing the distance between the operator and the RAM will decrease radiation exposure to personnel by the square of the distance. Handlers of radiopharmaceuticals may utilize techniques to increase distance, such as using remote handling tools, including within an ISO Class 5 PEC.

2.3 Shielding

Radiation exposure to personnel decreases with the use of shielding materials. Therefore, handlers of radiopharmaceuticals may use various shielding materials (e.g., lead, tungsten) in various configurations. The use of shielding, such as L-block, torso, vial, and syringe shields, is usually required throughout the radiopharmaceutical handling process, including within an ISO Class 5 PEC.

2.4 Radiation Contamination Control

RAM contamination (e.g., spills, drips, sprays, volatility) is an important concern for radiation protection. Therefore, various techniques and materials may be used by handlers of radiopharmaceuticals to minimize radioactive contaminations. For example, container contents are maintained at neutral or negative pressure, because positive pressure in a container is a common cause of radioactive contamination. Disposable absorbent pads are commonly used to contain such radioactive contamination and, when used in an ISO Class 5 PEC, the pads must be clean and low-lint. Vertical air flow, not horizontal, in a PEC is used to control contamination. When exposure to blood and other potentially infectious material is reasonably anticipated, some engineered needlestick prevention devices may pose a radiation hazard to employees. Policies must be implemented for handling biohazardous radioactive sharps while minimizing contamination.

RADIATION DETECTORS AND MEASURING DEVICES

Radiopharmaceuticals require measurement with a suitable radiation measuring device (e.g., dose calibrator). These and other necessary equipment, (e.g., monitors, bar code scanner, label printer) may be placed inside an ISO Class 5 PEC but should be placed in a manner that minimizes disruptions of airflow.

As per RAM license requirements, individuals must wear body and, as required, extremity dosimeters (e.g., a ring worn on a finger) for long-term monitoring of personnel radiation exposure. The body dosimeter should be worn underneath the gown. Any extremity dosimeter must be worn underneath gloves and must not interfere with proper fit of gloves.

3. IMMEDIATE USE OF STERILE RADIOPHARMACEUTICALS

The preparation and dispensing of sterile radiopharmaceuticals in a patient care setting may be handled as an immediate use practice. The information below describes the appropriate handling requirements for immediate use sterile radiopharmaceuticals in an ambient environment that lacks primary and secondary engineering controls (SEC) when intended for a single patient. Strict aseptic technique and limited beyond-use date (BUD) must be adhered to given the lack of engineering controls.

- Appropriate for preparation (including minor deviations) and/or dispensing that is limited to use for a single patient.
- Preparation (including preparations with minor deviations) components must be sterile, conventionally manufactured drug products (e.g., NDA, ANDA).
- Dispensing of drug products produced under an approved IND or RDRC protocol is allowed.
- Manipulations for any unit doses (e.g., decreasing the dosage, needle changes) or dispensing for one patient (e.g., withdrawing a dose) is allowed.
- Must be administered within 1 hour of the first container puncture or exposure of any critical site involved (e.g., syringe tip, needle hub or needle) to ambient air, whichever is first.
- All components involved (e.g., Tc-99m sodium pertechnetate syringe or vial, final prepared radiopharmaceutical kit vial, diluent vial) must be discarded within 1 hour of being punctured or after use for a single patient administration, whichever is first.
- Dose pooling (combining doses from two or more syringes to meet one patient's need) may be performed as immediate use. Any residual activity that remains must be immediately discarded and not utilized for any other patient.
- Follow hand hygiene and garbing in *4.4 Hand Hygiene and Garbing for Immediate Use Preparations*.
- Follow *10.4 Preparation of Radiolabeled Red Blood Cells for Immediate Use* for red blood cell labeling.
- Follow *12.2 Labeling* for labeling.
- Area for sterile preparation and/or dispensing must be functionally separate from nonsterile compounding area (e.g., radiolabeling food) during the time of use.
- Does not require a segregated radiopharmaceutical processing area (SRPA), classified area, or PEC.
- The number of steps or punctures is not limited.
- Does not require personnel to complete the aseptic qualifications as detailed in *4.1 Aseptic Qualifications* (e.g., aseptic technique training with documented assessment, media fill challenge, gloved fingertip testing).
- While adding a non-radioactive, sterile and commercially manufactured pharmaceutical (e.g., lidocaine) to a unit dose is otherwise considered compounding, it is allowed for immediate use purposes as long as all of the above are adhered to.
- Dose splitting (splitting a unit dose for administration to more than one patient) may not be performed as immediate use; if performed, dose splitting must be done in an ISO class 5 PEC in either an SRPA or in an ISO class 8 or better buffer area.

4. PERSONNEL QUALIFICATIONS, TRAINING, AND HYGIENE

Personnel must be trained to work with radiopharmaceuticals per the policies and standard operating procedures (SOPs) authorized by an ANP or AU physician. These individuals (e.g., nuclear medicine technologists or nuclear pharmacy technicians) must follow these policies and SOPs of the ANP or AU physician and work under their supervision. As appropriate, this should include blood-borne pathogens training.

Individuals entering a compounding area must be properly garbed and must maintain proper personal hygiene to minimize the risk of contamination to the environment and/or radiopharmaceuticals. Individuals who have a condition that may pose a higher potential of contaminating the radiopharmaceutical and the environment with microorganisms (e.g., rashes, sunburn, recent tattoos, oozing sores, conjunctivitis, or active respiratory infection) must report these conditions to their supervisor. The designated person is responsible for evaluating whether these individuals should be excluded from working in sterile processing areas before their conditions are resolved.

4.1 Aseptic Qualifications

Personnel must prove competency, as applicable to their job functions, prior to performing radiopharmaceutical aseptic tasks that are beyond immediate use. These qualifications may be conducted at a different site if all SOPs are identical for the applicable job function. These qualifications must be completed and documented initially, and then successfully repeated at intervals described below in *Timing of Reevaluation and Requalification* under the observation of a designated person and include the following:

- Aseptic technique training with a documented assessment (written or electronic)
- Garbing and hand hygiene, as defined by the policies and SOPs
- PEC cleaning and disinfecting
- Gloved fingertip and thumb sampling
- Media-fill testing

GLOVED FINGERTIP AND THUMB SAMPLING

Appropriate garbing, including sterile gloves, is necessary for personnel who enter and perform tasks in an ISO Class 5 PEC (e.g., aseptic manipulations, cleaning the PEC). Personnel that perform such functions must prove their competency in this process. Gloved fingertip and thumb sampling must be performed initially on both hands, immediately following hand-hygiene and garbing. Successful completion of initial gloved fingertip and thumb sampling is defined as zero colony-forming unis (cfu) and subsequent gloved fingertip and thumb sampling after media-fill testing is defined as ≤3 cfu (total for both hands).

- The gloved fingertip and thumb sampling must be performed with touch plates or other devices (e.g., plates, paddles, or slides) that contain a general microbial growth agar [e.g., trypticase soy agar (TSA) soybean–casein digest media] supplemented with neutralizing additives (e.g., lecithin and polysorbate 80) as this supports both bacterial and fungal growth
- Gloves must not be disinfected immediately before touching the sampling device, as this could cause a false-negative result
- Using a separate sampling device for each hand, a gloved fingertip and thumb sample from both hands must be collected by rolling finger pads and thumb pad over the agar surface
- The plates must be incubated in an incubator at 30°–35° for no less than 48 h, and then at 20°–25° for no less than 5 additional days

MEDIA-FILL TESTING

Media-fill testing is necessary for all personnel who prepare, compound, dispense, and repackage sterile radiopharmaceuticals. This testing must be reflective of the actual manipulations to be carried out by the individual and must simulate the most challenging and stressful conditions to be encountered in the worker's duties.

- Media-fill tests must be documented as defined by the facility's policies and SOPs.
- Media-fill tests should be performed at the end of a work session in the PEC.
- Media-fill tests must be performed with a commercial source of soybean–casein digest medium. Those performing sterile-to-sterile processing activities must start with sterile media. Those performing nonsterile-to-sterile compounding must use a nonsterile soybean–casein digest powder to make a solution. Dissolve nonsterile commercially available soybean–casein digest medium in nonbacteriostatic water to make a 3% nonsterile solution. Manipulate it in a manner that simulates nonsterile-to-sterile compounding activities. Prepare at least 1 container as the positive control to demonstrate growth promotion, which is indicated by visible turbidity upon incubation.
- The certificate of analysis (CoA) must include documentation of growth promotion testing for each lot of media used.
- Once the media-fill simulation is completed and the final containers are filled with the test medium, incubate media-filled containers in an incubator for 7 days at 20°–25° followed by 7 days at 30°–35° to detect a broad spectrum of microorganisms. Failure is indicated by visible turbidity or other visual manifestations of growth in the medium in 1 or more container–closure unit(s) on or before 14 days.
- In the event of failure, results of the evaluation and corrective actions must be documented and the documentation maintained to provide a record and long-term assessment of personnel competency. Documentation must at a minimum include the name of the person evaluated, evaluation date/time, media and components used including manufacturer, expiration date and lot number, starting temperature for each interval of incubation, dates of incubation, and the results.

4.2 Reevaluation, Retraining, and Requalification

REQUALIFICATION AFTER FAILURE

Personnel who fail visual observation of hand hygiene, garbing, and aseptic technique, gloved fingertip and thumb sampling, or media-fill testing must successfully pass reevaluations in the deficient area(s) before they can resume processing of sterile preparations. All failures, retraining, and reevaluations must be documented.

REQUALIFICATION PROGRAM

Personnel must successfully complete requalification in the core competencies listed in *4.1 Aseptic Qualifications*. Successful completion must be demonstrated through observation, written testing, and hands-on demonstration of skills.

TIMING OF REEVALUATION AND REQUALIFICATION

Visual observation: Personnel must be visually observed while performing hand hygiene, garbing SOPs, and aseptic technique procedures initially, and then at least once every 12 months.
Gloved fingertip and thumb sampling: Personnel must perform fingertip and thumb sampling 3 times initially, and then every 12 months (in conjunction with media-fill testing).
Media-fill testing: After initial qualification, conduct a media-fill test of all personnel engaged in sterile radiopharmaceutical processing at least every 12 months (in conjunction with gloved fingertip and thumb sampling).
Cleaning and disinfecting: Retrain and requalify personnel in the cleaning and disinfecting of sterile processing areas every 12 months or in conjunction with any change(s) in cleaning and disinfecting SOPs, whichever is sooner.
After a pause in sterile radiopharmaceutical processing: Personnel that have not performed radiopharmaceutical processing in more than 6 months must be requalified in all core competencies before resuming duties.

Sterile compounding using a nonsterile drug substance or components: Personnel who perform sterile compounding using a nonsterile drug substance or components (see *11.3 Sterile Compounding Using a Nonsterile Drug Substance or Components*) must be requalified in all core competencies every 6 months.

4.3 Ancillary Personnel

Personnel who are authorized to be within the sterile processing area and do not handle sterile preparations are not required to complete training on media-fill testing but are required to complete all other training and testing. Other personnel or visitors (e.g., auditors, regulators, student observers) must comply with garbing and gloving SOPs but do not need to prove competency.

4.4 Hand Hygiene and Garbing for Immediate Use Preparations

Radiopharmaceuticals may be prepared and dispensed as immediate use, and the precautions related to personal hygiene to be followed must include the following:

- Hand hygiene: Wash hands and arms to the wrists with soap and water or use a suitable alcohol-based hand rub with a time based on institution policies to reduce bioburden on the hands.
- Garbing: Immediately after hand hygiene, don a clean coat/gown that has not been exposed to a patient or patient care area, and either don sterile gloves or don nonsterile disposable gloves and then disinfect the gloves with sterile 70% IPA. [NOTE—A different lab coat must be worn to care for a patient than the coat/gown used for radiopharmaceutical preparation.]

4.5 Hand Hygiene and Garbing for Buffer Areas and Segregated Radiopharmaceutical Processing Area

In situations involving repackaging, dispensing, preparation, preparation with minor deviations, or compounding of sterile radiopharmaceuticals in an ISO Class 5 PEC, the following precautions related to personal hygiene are to be followed:

- Before entering the SRPA or buffer area, personnel must remove outer garments (e.g., bandanas, coats, hats, jackets, sweaters, vests); all cosmetics; all hand, wrist, and other exposed jewelry including piercings that could interfere with the effectiveness of the garbing (e.g., the fit of gloves, cuffs of sleeves, and eye protection). Nail products (e.g., artificial nails, polish, extenders) are prohibited. Natural nails must be kept neat and trimmed. Remove ear buds and headphones. Radiation dosimetry devices are allowed, as required by the RAM license.
- Do not bring electronic devices that are not necessary for compounding or other required tasks.
- Immediately before entering the SRPA or buffer area, remove visible debris from underneath fingernails under warm running water using a disposable nail cleaner. Personnel must wash hands and arms up the elbows with soap and water for at least 30 s and then dry hands using low-lint towels. Alternatively, hand washing may be performed after donning shoe covers, head/hair covers, and face mask, as described below.
- Personnel must don the following garb—shoe covers, head/hair/facial hair covers, face mask—in an order that eliminates the greatest risk of contamination, as defined in facility SOPs.
- If not already performed, remove visible debris from underneath fingernails under warm running water using a disposable nail cleaner. Personnel must then wash hands and arms up to the elbows with soap and water for at least 30 s and then dry hands using low-lint towels. Electronic hand dryers are not permitted.
- Personnel must then perform hand antisepsis cleansing using a suitable alcohol-based hand rub.
- Personnel must then don a low-lint gown with sleeves that fit snugly around the wrists and enclosed at the neck. Disposable gowns are preferred. If reusable gowns are used, a clean gown must be donned daily.
- Personnel must then aseptically don sterile, powder-free gloves. Gloves must completely and snugly cover the ends of the gown cuffs so that skin on the wrists and upper hands is completely enveloped.
- Because gloves may not remain sterile due to touching or handling potentially nonsterile materials, personnel must periodically apply sterile 70% IPA to gloves while balancing the risk of radioactivity contamination.
- Personnel must also routinely inspect the gloves that they are wearing for holes, punctures, radioactivity contamination, or tears. If a defect, radioactivity contamination, or malfunction is detected, personnel must immediately remove the gloves, repeat antiseptic hand cleansing using an alcohol-based hand rub, and don new sterile gloves.
- Direct personnel touch contamination is the most common source of microorganisms, so personnel must avoid touch contamination of container septa, needles, syringe and needle hubs, and other critical sites.

When personnel exit the buffer area or SRPA, shoe covers, head/hair covers, face masks, and gloves must be properly disposed of and new ones donned for each reentry into the buffer area or SRPA. Gowns may be re-used within the same shift if the gown is maintained in a classified area or in (or immediately outside of) the SRPA that minimizes contamination (e.g., away from sinks).

5. FACILITIES AND ENGINEERING CONTROLS

5.1 Facility Design and Environmental Controls

In addition to minimizing airborne contamination, sterile radiopharmaceutical facilities must be designed and controlled to provide a well-lighted and comfortable working environment (see *Physical Environments That Promote Safe Medication Use*

⟨1066⟩). The classified areas and SRPA must be continuously maintained at a temperature of 25° or cooler and should be continuously maintained at a relative humidity (RH) below 60% to minimize the risk for microbial proliferation and provide comfortable conditions for personnel attired in the required garb. The temperature and humidity must be monitored in the classified areas each day that it is used, either manually or by a continuous recording device. The results of the temperature and humidity readings must be documented at least once daily or stored in the continuous recording device, and must be retrievable. The temperature and humidity readings must be reviewed as described in the facility's SOPs. Free-standing humidifiers/dehumidifiers and air conditioners must not be used within the classified area or SRPA. Temperature and humidity monitoring devices must be verified for accuracy at least every 12 months or as required by the manufacturer.

The designated person is responsible for ensuring that each area related to sterile radiopharmaceutical processes meets the classified air quality standard appropriate for the activities to be conducted in that area. They must also ensure that the ISO Class 5 PECs are located, operated, maintained, monitored, and certified to have appropriate air quality.

TYPES OF SECONDARY ENGINEERING CONTROLS AND DESIGN

Due to the interdependence of the various areas or areas that make up a sterile radiopharmaceutical processing facility, it is essential to define and control the dynamic interactions permitted between areas. When designing doors, consider the placement of door closures, door surfaces, and the movement of the door, all of which can affect airflow. Tacky surfaces must not be used in ISO-classified areas.

The PEC must be located in a SEC, which may be either an ISO-classified buffer room with ante-room or an SRPA, in a manner that minimizes conditions that could increase the risk of microbial contamination. For example, strong air currents from opened doors, personnel traffic, or air streams from the HVAC system(s) can disrupt the unidirectional airflow of an open-faced PEC such as a laminar airflow workbench (LAFW) or biological safety cabinet (BSC). The ISO-classified ante-room and buffer area must be separated from the surrounding unclassified areas of the facility with fixed walls and doors. Facility design and controls must be in place to minimize the flow of lower-quality air into the more controlled areas. Air supplied to the classified areas must be introduced through HEPA filters that are located in the ceiling. Returns must be low on the wall unless a visual smoke study demonstrates an absence of stagnant airflow where particulate will accumulate. A smoke study of the PEC must be repeated whenever a change to the placement of the PEC within the area is made. The classified areas must be equipped with a pressure-differential monitoring system. The ante-room must have a line of demarcation to separate the clean side from the less clean side. The ante-room is entered through the less clean side, and the clean side is the area closest to the buffer area. Required garb must be worn prior to crossing the line of demarcation (see *4. Personnel Qualifications, Training, and Hygiene*).

A PEC may be located within an unclassified area, without an ante-room or buffer area. This type of design is called an SRPA. Only sterile radiopharmaceutical preparation, preparation with minor deviations, dispensing, and repackaging may be performed in an SRPA. If the SRPA meets ISO Class 8 total airborne particle count specifications, it can also be used for storage and elution of non-direct infusion radionuclide generators (e.g., Tc-99m). The SRPA must be located away from unsealed windows, doors that connect to the outdoors, and traffic flow which may adversely affect the air quality in the PEC. The impact of activities that will be conducted around or adjacent to the SRPA must be considered carefully when designing such an area. A visible perimeter must establish the boundaries of the SRPA. Access to the SRPA must be restricted to authorized personnel and required materials. An SRPA must not be located adjacent to environmental control challenges.

It is also critical to control materials (e.g., supplies and equipment) as they move from classified areas of lower quality to those of higher quality (e.g., ISO Class 8 ante-room to ISO Class 7 buffer area to ISO Class 5 PEC) to prevent the influx of contaminants. Airlocks and interlocking doors can be used to facilitate better control of air flow between areas of differing ISO classification (e.g., between the buffer area and ante-room), or between a classified area and an unclassified area (e.g., between the ante-room and an unclassified area such as a hallway) See *5.7 Environmental Controls* for a description of air pressure differentials. If a pass-through is used, both doors must never be opened at the same time, which may be achieved using interlocking mechanisms.

THE RADIOPHARMACEUTICAL PROCESSING ENVIRONMENT

The PEC must be certified to meet ISO Class 5 or better conditions (see *Table 1*) and must be designed to minimize microbial contamination during processing of radiopharmaceuticals under dynamic operating conditions.

The airflow in the PEC must be unidirectional (laminar flow), and because of the particle collection efficiency of the filter, the "first air" at the face of the filter is, for the purpose of aseptic processing, free from airborne particulate contamination. HEPA-filtered air must be supplied in the direct processing area (DPA) (ISO Class 5; see *Table 1*) at a velocity sufficient to sweep particles away from aseptic processing areas and maintain unidirectional airflow as much as possible during operations, given the limitations added from the radiation shielding in the DPA. Proper design and control prevents turbulence and stagnant air in the DPA. In situ air pattern analysis via smoke studies must be conducted at the critical area to demonstrate unidirectional airflow and sweeping action under dynamic conditions.

Table 1. ISO Classification of Particulate Matter in Area Air[a]

ISO Class	Particle Count[b] /m^3
3	35.2
4	352
5	3520
6	35,200
7	352,000
8	3,520,000

[a] Adapted from ISO 14644-1, Clean areas and associated controlled environments—Part 1: Classification of air cleanliness by particle concentration.
[b] Limits for number of particles ≥0.5 µm measured under dynamic operating conditions.

TYPES OF PECS AND PLACEMENT

Proper placement of the PEC is critical to ensuring an ISO Class 5 environment for preparing radiopharmaceuticals. Placement of the PEC must allow for cleaning around the PEC.

A PEC provides an ISO Class 5 or better environment for sterile radiopharmaceuticals. The unidirectional airflow within the PEC helps protect the DPA from process-generated contamination of an aseptic processing environment. The unidirectional airflow within the PEC helps protect the DPA from process-generated contamination (e.g., opening wrappings of sterile containers, worker movement, etc.) as well as from outside sources.

Laminar airflow workbench (LAFW): An LAFW used for preparing radiopharmaceuticals must provide vertical unidirectional HEPA-filtered airflow. In cases where the LAFW is located within the segregated containment area of a hot-cell, it is acceptable for a horizontal unidirectional HEPA-filtered airflow pattern to be utilized.

Biological safety cabinet (BSC) Class II: A BSC Class II is a cabinet with an open front, inward airflow, downward unidirectional HEPA-filtered airflow, and HEPA-filtered exhaust. The BSC is designed to provide worker protection from exposure to biohazardous material and to provide an ISO Class 5 or better environment for preparing sterile radiopharmaceuticals.

Placement of PEC: The PEC must be located out of traffic patterns and away from area air currents that could disrupt the intended airflow patterns inside the PEC. If used only to prepare, prepare with minor deviations, dispense, or repackage sterile radiopharmaceuticals the ISO Class 5 PEC may be placed in an unclassified SRPA. If used to compound sterile radiopharmaceuticals, the PEC must be located within an ISO Class 7 or better buffer area with an ISO Class 8 or better ante-room. A dynamic airflow smoke pattern test must be performed initially and at least every 6 months to ensure that the PEC is properly placed into the facility and that workers understand how to utilize the unidirectional airflow to maintain first air as much as possible given the limitations added from the radiation shielding in the DPA.

AIR-EXCHANGE REQUIREMENTS

For classified areas, adequate HEPA-filtered airflow to the buffer area(s) and ante-room(s) is required to maintain the appropriate ISO classification during processing activities. Airflow is measured in terms of the number of HEPA-filtered air changes per hour (ACPH). The ACPH may need to be higher to maintain the required ISO classification and microbial state of control depending on these factors: the number of personnel permitted to work in the area, the number of particulates that may be generated from activities and processes in the area, the equipment located in the area, the area pressure, and the effects of temperature. The summary of ACPH requirements is listed in *Table 2*.

A minimum of 30 total HEPA-filtered ACPH must be supplied to ISO Class 7 areas.

- The total HEPA-filtered air change rate must be adequate to maintain ISO Class 7 under dynamic operating conditions considering factors listed above
- At least 15 ACPH of the total air change rate in a room must come from the HVAC through HEPA filters located in the ceiling
- The HEPA-filtered air from the PEC, when added to the HVAC-supplied HEPA-filtered air, increases the total HEPA-filtered ACPH to at least 30 ACPH
- If the PEC is used to meet the minimum total ACPH requirements, the PEC must not be turned off except for maintenance
- The ACPH from HVAC, ACPH contributed from the PEC, and the total ACPH must be documented on certification reports

A minimum of 20 ACPH of HEPA-filtered air must be supplied to ISO Class 8 areas.

- The total HEPA-filtered air change rate must be adequate to maintain ISO Class 8 under dynamic operating conditions considering factors listed above
- At least 15 ACPH of the total air change rate in a room must come from the HVAC through HEPA filters located in the ceiling
- Ante-rooms where activity levels are high may require more HEPA-filtered ACPH to maintain ISO Class 8 under dynamic operating conditions
- The total ACPH must be documented on certification reports

Table 2. Summary of ACPH Requirements for Sterile Radiopharmaceutical Processing

Processing Area	ACPH Requirement
Unclassified SRPA	No requirement
ISO Class 7 area	≥30 ACPH
ISO Class 8 area	≥20 ACPH

5.2 Creating Areas to Achieve Easily Cleanable Conditions

CLASSIFIED AREAS

The surfaces of ceilings, walls, floors, doors, door frames, fixtures, shelving, work surfaces, counters, and cabinets in the classified area must be smooth, impervious, free from cracks and crevices, and non-shedding, so they can be cleaned and disinfected, and to minimize spaces in which microorganisms and other contaminants can accumulate. Surfaces should be resistant to damage by cleaning agents, disinfectants, and tools used to clean. Junctures between the ceiling and the walls and

between the wall and the floor must be sealed to eliminate cracks and crevices where dirt can accumulate. If ceilings consist of inlaid panels, each panel must be caulked or otherwise sealed and secured to seal them to the support frame.

Walls must be constructed of or covered with a durable material (e.g., epoxy-painted walls or heavy-gauge polymer) and the integrity of the surface must be maintained. Panels must be joined together and sealed to each other and the support structure. Floors must include coving to the sidewall or the juncture between the floor and wall must be caulked. Floors must include coving to the sidewall. Classified areas should minimize dust-collecting overhangs such as utility pipes and ledges such as windowsills. If overhangs or ledges are present, they must be easily cleanable. The exterior lens surface of ceiling light fixtures must be smooth, mounted flush, and sealed. Any other penetrations through the ceiling or walls must be sealed.

SRPA

The SRPA and all surfaces (e.g., walls, floors, counters, equipment) within the SRPA must be clean, uncluttered, and dedicated to sterile radiopharmaceutical processing activities. Surfaces in the SRPA should be smooth, impervious, free from cracks and crevices, and non-shedding, so they can be easily cleaned and disinfected, and to minimize spaces in which microorganisms and other contaminants can accumulate. Surfaces should be resistant to damage by cleaning agents, disinfectants, and tools used to clean. Dust-collecting overhangs such as utility pipes and ledges such as windowsills should be minimized. If overhangs or ledges are present, they must be easily cleanable.

5.3 Water Sources

The facility where sterile radiopharmaceuticals are prepared must be designed so that activities such as hand hygiene and garbing should not adversely affect the ability of the PEC to function as designed. Sinks should enable hands-free use with a closed system of soap (i.e., non-refillable) to minimize the risk of extrinsic contamination. In facilities with an ante-room and buffer area, the sink used for hand hygiene may be placed either inside or outside of the ante-room. If the sink is located outside of the ante-room, it must be located in a clean space to minimize the risk of bringing in contaminants into the ante-room. If the sink is located inside the ante-room, it may be placed on either the clean side or the less-clean side of the ante-room. [NOTE—The order of hand washing and garbing would depend on the placement of the sink (see *4.5 Hand Hygiene and Garbing for Buffer Areas and Segregated Radiopharmaceutical Processing Area*).] The buffer area must not contain plumbed water sources [e.g., sink(s), eyewash(es), shower(s), or floor drain(s)]. The ante-room must not contain floor drain(s). If installed, sprinkler systems in classified areas should be recessed and covered, and should be easily cleanable. In a facility with an SRPA design, the sink must be accessible but located at least 1 m from the PEC and generators, if present. The sink must not be located inside the perimeter of the SRPA.

5.4 Placement and Movement of Materials

Only furniture, equipment, and other materials necessary are permitted in the classified area or SRPA and they should be low-shedding and easily cleaned and disinfected. Their number, design, location, and manner of installation must not adversely impact environmental air quality and must promote effective cleaning and disinfecting. No shipping carton(s) or other corrugated or uncoated cardboard are allowed in the classified area or SRPA.

Carts used to transport components or equipment into classified areas must be constructed from nonporous materials with cleanable casters and wheels. All items must be wiped with low-lint wipers and an appropriate disinfectant by personnel wearing gloves before they are brought into the clean side of ante-room(s), pass-through(s), into an SRPA or into an ISO 5 PEC. However, constraints that would lead to excessive radiation exposure to radiation for workers and thereby be contradictory to following ALARA safety principles (e.g., the wiping of unshielded sources of radioactive material) might preclude this from occurring. In a classified area, carts must not be moved from the dirty side to the clean side of the ante-room unless the entire cart, including casters, is cleaned and disinfected.

5.5 Classified Areas

Activities and tasks carried out within the buffer area must be limited to only those necessary. Food, drinks, and materials exposed in patient care and treatment areas must not enter ante-rooms or buffer areas. When processing activities require the manipulation of blood-derived or other biological material (e.g., radiolabeling patient's or donor's blood cells), the manipulations must be clearly separated from routine material-handling procedures and equipment used in radiopharmaceutical preparation activities, and they must be controlled by specific SOPs to avoid any cross-contamination.

5.6 Remote Aseptic Processing Involving a Hot-Cell

A hot-cell device provides an inherent physical segregation for the ISO Class 5 aseptic processing area. If the hot-cell is located in an ISO-classified space, personnel must garb according to requirements listed in *4.5 Hand Hygiene and Garbing for Buffer Areas and Segregated Radiopharmaceutical Processing Area*. In settings where tasks are carried out within the hot-cell enclosure not within an ISO-classified space by remote means (i.e., no direct intervention by personnel into the ISO Class 5 space), it is not necessary for personnel to don the garbing described in *4.5 Hand Hygiene and Garbing for Buffer Areas and Segregated Radiopharmaceutical Processing Area* to carry out these aseptic manipulations or to perform other routine tasks in the general area where the hot-cell is located. If hand and arm incursions into the interior of the hot-cell might be necessary for personnel to stage the required materials and supplies, the personnel must garb in relation to the contamination risk associated with the individual hot-cell/ISO Class 5 relationship.

For situations where a PEC device is located within a hot-cell, dynamic airflow smoke pattern tests must show that the staging of supplies and materials in the demarcated PEC area does not allow the influx of unclassified air into the PEC. Personnel may

be garbed in nonsterile gloves and a low-particulate lab coat for interventions that are outside of the PEC. A failure of the airflow smoke pattern test requires personnel to garb in accordance with *4.5 Hand Hygiene and Garbing for Buffer Areas and Segregated Radiopharmaceutical Processing Area* for all incursions into the hot-cell.

For situations where the hot-cell is an integrated HEPA filtration system with a clear demarcated area that is a PEC, dynamic airflow smoke pattern tests must show that the staging of supplies and materials into the demarcated PEC area does not allow the influx of less than ISO Class 5 quality air into the PEC. Personnel may be garbed in nonsterile gloves and a low-particulate lab coat for interventions that are outside of the PEC. A failure of the airflow smoke pattern test requires personnel to garb in accordance with *4.5 Hand Hygiene and Garbing for Buffer Areas and Segregated Radiopharmaceutical Processing Area* for all incursions into the PEC.

Since other hot-cell/PEC configurations and technologies may exist, verification (either by airflow smoke pattern tests or other manufacturer specified methods) must ensure, upon each certification, that the staging of materials and supplies does not allow for the intrusion of less than ISO Class 5 air into the designated ISO Class 5 space. A failure of the airflow smoke pattern test requires personnel to garb in accordance with *4.5 Hand Hygiene and Garbing for Buffer Areas and Segregated Radiopharmaceutical Processing Area* for all incursions into the hot-cell.

5.7 Environmental Controls

All RAM users must comply with the conditions specified in their approved RAM license application and regulations, and RAM license conditions may supersede the following requirements for environmental controls described in this section. Pass-through enclosures for transferring radiopharmaceuticals from controlled handling areas (e.g., buffer area) should be designed to provide reasonable balance between maintenance of air quality and other worker safety concerns (e.g., radiation exposure, physical injury from lifting heavy shielded cases). At a minimum, there must be a mechanical system or SOP in place that ensures that both doors cannot be open at the same time. There may be both positive and negative air pressure within the facility; positive pressure to minimize the potential of microbial contamination in sterile drug preparation areas, and negative pressure to minimize potential radioactive contamination from volatile or airborne radiopharmaceuticals. Positive pressure environments must have a minimum differential positive pressure of 0.02-inch water column between each ISO-classified area (e.g., between the buffer area and ante-room). The pressure differential between the ante-room and the unclassified area must be no less than a positive 0.02-inch water column. Refer to the RAM license for negative pressure requirements. For preparation of sterile radiopharmaceuticals, consideration of both concerns could be addressed as follows:

1. Buffer area, if present, must be positive pressure compared to the ante-room
2. Ante-room, if present, must be positive pressure compared to unclassified portions of the restricted area
3. Restricted area, in the presence of volatile or airborne radiopharmaceuticals, must be negative pressure compared to the unrestricted area
4. SRPA must be negative pressure compared to unrestricted areas in the presence of volatile or airborne radiopharmaceuticals (e.g., I-131 sodium iodide and Xenon).

Various environmental controls for various preparation scenarios (see *Table 7* for maximum BUDs for differing environments) are described in the following sections. *Table 1* details the limits for particle counts for each specific ISO classification.

ESTABLISHING AND MAINTAINING PRESSURE DIFFERENTIALS

Any time a pressure differential is required, a pressure monitoring device is required. In a classified area, a pressure differential monitoring system must be used to continuously monitor the pressure differential between the ante-room(s) and buffer area(s) and between the ante-room and the general environment outside the classified area(s) or area(s). The results from the pressure monitoring system must be reviewed and documented at least daily on days the area is used. All pressure monitoring devices must be tested for accuracy and required performance at least every 6 months.

AMBIENT ATMOSPHERE FOR IMMEDIATE USE PREPARATIONS

The following requirements should be met in ambient atmosphere environments:

- Non-patient care space, functionally separate (not necessarily a different area) from the patient care area, such as a radiopharmaceutical handling space, or hot lab, in a hospital, clinic, or mobile coach
- A designated area for medication preparation that is clean and free from clutter
- Low traffic (i.e., limited number of people going in and out or moving around the area during times that radiopharmaceutical processing is being carried out)

SRPA WITH VERTICAL FLOW ISO CLASS 5 PEC(S) FOR RADIOPHARMACEUTICAL PREPARATIONS

An SRPA with vertical ISO Class 5 PECs must meet the following requirements:

- Area surrounding the PEC may be ambient (unclassified) atmosphere
- Area must be clean, uncluttered, and dedicated to the processing of radiopharmaceuticals
- Appropriate for preparation, preparation with minor deviations, repackaging, and dispensing of radiopharmaceuticals

An area that meets ISO Class 8 total airborne particle-count specifications may be used to store and elute non-direct infusion radionuclide generators (e.g., Tc-99m).

AN ISO CLASS 8 BUFFER AREA WITH VERTICAL FLOW ISO CLASS 5 PEC(S) WITH AN ADJACENT ISO CLASS 8 ANTE-ROOM

This environment is appropriate for all activities listed in *SRPA with Vertical Flow ISO Class 5 PEC(s) for Radiopharmaceutical Preparations*.

AN ISO CLASS 7 BUFFER AREA WITH VERTICAL FLOW ISO CLASS 5 PEC(S) WITH AN ADJACENT ISO CLASS 8 OR BETTER ANTE-ROOM

This environment is appropriate for all activities listed in *An ISO Class 8 Buffer Area with Vertical Flow ISO Class 5 PEC(s) with an Adjacent ISO Class 8 Ante-Room* and sterile compounding.

HOT-CELL

This environment is appropriate for all activities listed in *SRPA with Vertical Flow ISO Class 5 PEC(s) for Radiopharmaceutical Preparations*.

CERTIFICATION OF PECS AND ENVIRONMENT IN WHICH THE PEC IS LOCATED

Certification of the classified areas, including the PEC, must be performed initially and recertification must be performed at least every 6 months using procedures outlined in the current Controlled Environment Testing Association (CETA) certification guide for *Sterile Compounding Facilities*, or an equivalent guideline, and must include the following:

- Airflow testing: To determine acceptability of the air velocity, the air exchange rate, and area pressure cascade to ensure that air consistently flows from most to least clean areas, and that the appropriate quality of air is maintained under dynamic operating conditions.
- HEPA filter integrity testing: HEPA filters must be leak tested after installation and as part of recertification.
- Total particle counts testing: Conducted under dynamic operating conditions using calibrated electronic equipment.
- Smoke visualization studies: Performed under either simulated or dynamic operating conditions to demonstrate unidirectional airflow and sweeping action over and away from the preparation(s).

In cases where technologies exist for hot-cell and PEC configurations that are not consistent for certification by the current CETA standards, other equivalent means for certifying the PEC may be performed and documented per facility SOPs. In this case, the PEC must maintain the environmental equivalent for total particle counts and the protection of the ISO Class 5 area from intrusions of lesser controlled air.

DAILY MONITORING OF ENVIRONMENT

The temperature and humidity must be monitored in the SRPA or area containing a hot-cell, and if in a classified area the pressure must monitored, each day that preparations are made, either manually or by a continuous recording device. These include:

- Relative humidity should be kept at 60% or lower
- Temperature and relative humidity continuous readings must be confirmed daily to have remained within the acceptable range
- Excursions must be documented and, if applicable, appropriate corrective actions taken
- Temperature monitoring devices must be verified for accuracy every 12 months or as required by the manufacturer
- Monitoring of pressure differentials must be performed

See *Packaging and Storage Requirements* ⟨659⟩ for information on controlled area temperature and allowable excursions.

6. MICROBIOLOGICAL AIR AND SURFACE MONITORING

An effective air and surface monitoring program provides information on the environmental quality of the classified areas where sterile radiopharmaceuticals are processed. The program identifies environmental quality trends over time, potential routes of microbiological contamination, and allows for implementation of corrective actions to prevent microbiological contamination of the radiopharmaceuticals. Facilities must develop and implement written air and surface monitoring procedures for all sterile radiopharmaceutical classified areas. Air and surface monitoring results and the corrective actions must be documented, and records must be readily retrievable as required by jurisdictional laws and regulations.

6.1 General Monitoring Requirements

The goals of an air and surface monitoring program are to determine whether microbiological contamination is present at unacceptable levels and to assess whether proper personnel practices are being followed, cleaning and disinfecting agents are effective, and environmental quality is maintained. The microbiological air and surface monitoring program must include viable impact volumetric airborne particulate sampling and surface sampling.

Air and surface sampling must be performed initially for classified areas in a facility to establish a baseline level of environmental quality. After initial sampling, the classified areas must be monitored according to the minimum frequencies described in this section to ensure that the environment remains in a suitable state for aseptic processing tasks.

The air and surface monitoring program involves the collection and evaluation of samples from various air and surface locations to detect viable microbiological contaminants. The data are then used to assess risks for contamination, potential

routes of contamination, and the adequacy of cleaning and disinfection techniques and agents specified in the facility SOPs. Regular review of the sampling data must be performed to detect trends such as elevated levels of microbial bioburden, elevated levels of nonviable particulates, or other adverse changes within the environment. Evaluating results collected over a period of time can be useful in identifying trends or determining that a significant change has occurred, even when the results fall within the specified limits.

In addition, results must be reviewed in conjunction with personnel data (i.e., training records, visual observations, competency assessments) to assess the state of control and to identify potential risks of contamination. Prompt corrective action in response to any adverse findings is required to maintain the necessary environmental quality for handling sterile radiopharmaceutical. Data must also be reviewed following corrective actions to confirm that the actions taken have been effective in achieving the required air and surface quality levels (see *Table 3* and *Table 4*).

Air and surface sampling must be conducted during actual or simulated dynamic operating conditions to confirm that the required environmental quality in classified areas is maintained. Due to radiation exposure concerns for the workers involved, it is permissible for sampling to be carried out at the conclusion of sterile radiopharmaceutical processing but prior to cleaning and disinfecting the surface area. In this case, simulated tasks that are reflective of the routine aseptic activities are performed. In addition to the specific sampling frequencies described in this section, sampling must be performed in any of the following circumstances:

- In conjunction with the certification of new facilities and equipment
- After any modification of facilities or equipment
- In response to identified problems (e.g., positive growth in sterility tests of compounded radiopharmaceuticals)
- In response to identified trends (e.g., repeated positive gloved fingertip sampling results or failed media-fill testing involving more than one operator where a review of the operator technique shows no reasonable flaws in process; repeated observations of air or surface contamination)
- In response to changes that could impact the controlled area environments (e.g., significant change in cleaning process or the agents involved)

To obtain an air and surface sample that is representative of the typical aseptic operating conditions at the facility, air and surface sampling must be conducted under dynamic or simulated dynamic operating conditions in all PECs and classified areas. If conducted during actual sterile processing, the monitoring program must be designed and conducted in a manner that minimizes the chance that the sampling itself will contribute to contamination of the sterile radiopharmaceutical(s) or the environment.

The air and surface monitoring program must be clearly described in the established SOPs of the facility and must include a diagram of the sampling locations, SOPs for collecting samples, frequency of sampling, size of samples (e.g., surface area, volume of air), time of day of sampling in relation to activities in the classified areas, and action levels that will trigger corrective action. The locations of sampling should be carefully selected based on their relationship to the activities performed in the area. It is important to obtain samples from locations that pose the highest possible contamination risk to the sterile radiopharmaceuticals involved with the operation's processes and that are likely to be representative of the conditions throughout the area.

Evaluating results collected over a period of time can be useful in identifying trends or determining that a significant change has occurred, even when the results fall within the specified limits.

It is important that personnel who operate the equipment be trained in the proper operation of the air and surface sampling equipment to ensure accurate and reproducible sampling. All air sampling devices must be serviced and calibrated as recommended by the manufacturer.

6.2 Monitoring Air Quality for Viable Airborne Particles

A monitoring program for viable airborne particles must be developed and implemented to assess microbiological air quality in all classified areas.

VIABLE AIR SAMPLING: TIMING AND LOCATIONS

Volumetric active air sampling of all classified areas (e.g., ISO Class 5 PEC and ISO Class 7 and 8 areas) using an impaction device must be conducted during dynamic operating or simulated operating conditions at least every 6 months.

Air sampling sites must be selected in all classified areas. When conducting sampling of the PEC, care should be taken to avoid disturbing unidirectional airflow if taken during actual sterile processing activities. Viable air sampling must include:

1. Follow the manufacturer's instructions for operation of the air sampling device, including placement of media.
2. Using the sampling device, test at least 1 cubic meter or 1000 liters of air from each location sampled.
3. At the end of the sampling, retrieve the media plates/devices and cover.
4. Invert the media and incubate at 30°–35° for no less than 48 hours. Examine for growth. Record the total number of discrete colonies of microorganisms on each plate as cfu/m^3 of air on an environmental sampling form based on sample type (i.e., viable air). Include sample location and date.
5. Then incubate the inverted media at 20°–25° for no less than 5 additional days. Examine the media plates for growth. Record the total number of discrete colonies of microorganisms on each plate as cfu/m^3 of air on an environmental sampling form based on sample type (i.e., viable air). Include sample location and date.

Alternatively, to shorten the overall incubation period, two samples may be collected for each sample location and incubated concurrently. Both samples could be TSA or one sample could be TSA and the other fungal media [e.g., malt extract agar (MEA) or sabouraud dextrose agar (SDA)]. Incubate each sample in a separate incubator. Incubate one sample at 30°–35° for no less than 48 hours, and incubate the other sample at 20°–25° for no less than 5 days. Fungal media samples must be incubated at

20°–25° for no less than 5 days. Count the total number of discrete colonies of microorganisms on each sample, and record these results as cfu per sample.

Record the results of the sampling on an environmental sampling form based on sample type (i.e., viable air) and include the sample location, and sample date.

A general microbiological growth medium that supports the growth of bacteria and fungi must be used (e.g., TSA medium). CoA(s) from the manufacturer must verify that the medium meets the expected growth promotion, pH, and sterilization requirements. Samples must be incubated in a temperature monitored incubator with a calibrated measuring device. The incubator temperature must be monitored during incubation, either manually or by a continuous recording device, and the results must be reviewed and documented. Incubators used for microbiological testing must be placed in a location outside of any classified area or SRPA and kept away from areas where compounding or sterile processing activities are carried out. All sampling activities must be performed by trained individuals.

DATA EVALUATION AND ACTION LEVELS

Evaluate cfu counts against the action levels in *Table 3* and in relation to previous data to identify adverse results and/or trends. If two pieces of media were collected at a single location, all recovered growth on each must be documented and action levels are applied individually to each plate/device (i.e., results from each cubic meter of air sampled must be compared to the action level for that area). If levels measured during the viable air monitoring program exceed the levels in *Table 3* for the ISO classification levels of the area sampled, the cause must be investigated and corrective action must be taken. The corrective action plan must be dependent on the cfu count and the microorganism recovered. Some examples of corrective action include process or facility improvements, personnel training, cleaning and disinfecting, or HEPA filter replacement and/or repair, or reducing the BUD of the radiopharmaceutical during investigation and while carrying out the corrective action plan. The extent of the investigation should be consistent with the deviation and should include an evaluation of trends. The corrective action plan must be documented. If levels measured during viable air sampling exceed the levels in *Table 3*, an attempt must be made to identify any microorganism recovered to the genus level (see *Microbial Characterization, Identification, and Strain Typing* ⟨1113⟩) with the assistance of a qualified individual (e.g., microbiologist or industrial hygienist).

Table 3. Action Levels for Viable Airborne Particle Air Sampling[a]

ISO Class	Air Sampling Action Levels [cfu/m³ (1000 L) of air per plate]
5	>1
7	>10
8	>100

[a] Adapted from *Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice*. US Department of Health and Human Services, Food and Drug Administration (FDA), September 2004.

6.3 Monitoring Surfaces for Viable Particles

Surface sampling is an important component of the maintenance of a suitably controlled environment for sterile radiopharmaceutical processing, especially because transfer of microbial contamination from improperly disinfected work surfaces (e.g., via inadvertent touch contact by personnel) is a potential source of contamination of the radiopharmaceutical(s). Surface sampling is useful for evaluating facility cleaning and material handling procedures, work surface cleaning and disinfecting procedures, and personnel competency in work practices such as proper cleaning and disinfection. All sampling sites and procedures must be described in the facility's SOP.

SURFACE SAMPLING: TIMING AND LOCATIONS

Surface sampling of all classified areas and all PECs must be conducted at least monthly for the detection of microbial contamination. Each classified area must be sampled (see *Microbiological Control and Monitoring of Aseptic Processing Environments* ⟨1116⟩). The DPA of the PEC, and any equipment permanently contained in the PEC, must be sampled. Staging or work surfaces in classified areas near the PEC, frequently touched surfaces in classified areas, and pass-through enclosure(s) for all classified areas are to be evaluated to determine the locations that pose the greatest risk of harboring microbial contamination.

Surface sampling must be performed at the end of the radiopharmaceutical aseptic activities or shift, but before the area has been cleaned and disinfected. However, radiopharmaceutical personnel must also consider the appropriate exposure and contamination prevention measures prior to and while collecting samples. If the worker assesses that the risk for exposure is not in conformance with ALARA safety standards, measures must be taken to eliminate the risk (e.g., implementation of appropriate shielding, performing the sampling at a later time or alternate day).

SAMPLING PROCEDURES

Surface sampling devices (e.g., plates, paddles, or slides) containing microbial growth media must be used for sampling flat surfaces. CoAs from the manufacturer must verify that the media meet the expected growth promotion, pH, and sterilization requirements. Surface sampling devices must contain general microbial growth media (e.g., TSA) supplemented with neutralizing additives (e.g., lecithin and polysorbate 80) to neutralize the effects of any residual disinfecting agents. If used, contact plates must have a raised convex surface. Sterile swabs wetted with sterile water or a sterile neutralizing buffer may be

used when sampling irregular surfaces and difficult-to-reach locations, such as crevices, corners, and spaces between surfaces. After sampling, the sampled area must be thoroughly cleaned and disinfected.

Use the following procedures for surface sampling on flat surfaces:

1. Remove the cover from the surface sampling device. Firmly press, using a rolling motion, if possible, the media surface onto the surface to be sampled. The surface sampling device will leave a residue of growth medium on the sample site. After sampling, use sterile 70% IPA to remove residue. Cover each surface sampling device.
2. If using plates, invert the plates.
3. Incubate the surface sampling devices at 30°–35° for no less than 48 hours. Examine for growth. Record the total number of discrete colonies of microorganisms on each media device as cfu/sample on an environmental sampling form based on sample type (i.e., surface). Include sample location and date.
4. Incubate the device at 20°–25° for no less than 5 additional days. Examine the media plates for growth. Record the total number of discrete colonies of microorganisms (cfu/sample) on the environmental sampling record based on sample type (i.e., surface). Include sample location and date.

Alternatively, to shorten the overall incubation period, two samples may be collected for each sample location.

1. Both samples could be TSA or one sample could be TSA and the other fungal media (e.g., MEA or SDA).
2. Incubate each sample in a separate incubator. Incubate one sample at 30°–35° for no less than 48 hours, and incubate the other sample at 20°–25° for no less than 5 days.
3. If fungal media are used as one of the samples, incubate the fungal media sample at 20°–25° for no less than 5 days.
4. Count the total number of discrete colonies of microorganisms on each sample, and record these results as cfu per sample. Record the results of the sampling.
5. Record the results of the sampling.

DATA EVALUATION AND ACTION LEVELS

Evaluate cfu counts against the action levels in *Table 4* and examine counts in relation to previous data to identify adverse results or trends. If two devices were collected at a single location, all recovered growth on each must be documented and action levels are applied to each piece of media individually (i.e., results from each sampling device must be compared to the action level for the area). If levels measured during surface sampling exceed the levels in *Table 4* for the ISO classification levels of the area sampled, the cause must be investigated and corrective action must be taken. Data collected in response to corrective actions must be reviewed to confirm that the actions taken have been effective. The corrective action plan must be dependent on the cfu count and the microorganism recovered. Examples of corrective action include process or facility improvements, personnel training, cleaning and disinfecting, or HEPA filter replacement and/or repair, or reducing the BUD of the radiopharmaceutical(s) during investigation and while carrying out the corrective action plan. The extent of the investigation should be consistent with the deviation and should include an evaluation of trends. The corrective action plan must be documented. If levels measured during surface sampling exceed the levels in *Table 4*, an attempt must be made to identify any microorganism recovered to the genus level (see ⟨1113⟩) with the assistance of a qualified individual (e.g., microbiologist or industrial hygienist).

Table 4. Action Levels for Surface Sampling

ISO Class	Surface Sampling Action Levels (cfu/device or swab)
5	>3
7	>5
8	>50

7. CLEANING AND DISINFECTING

Cleaning and disinfecting are important because surfaces in classified areas and SRPAs are a potential source of microbial contamination of sterile radiopharmaceuticals. The process of cleaning involves removing organic and inorganic residues from surfaces, usually with a manual or mechanical process and a cleaning agent. The process of disinfecting involves destruction of microorganisms, usually with a chemical or physical agent. Surfaces must be cleaned prior to being disinfected unless an Environmental Protection Agency (EPA)-registered (or equivalent) one-step disinfectant cleaner is used to accomplish both the cleaning and disinfection in one step. After cleaning and disinfecting or the application of a one-step disinfectant cleaner in a PEC, apply sterile 70% IPA to remove any residue.

Cleaning and disinfecting surfaces should occur at the minimum frequencies specified in *Table 5* or if activities are not performed daily, cleaning and disinfecting must be completed before initiating activities. The act of reducing or removing radioactivity (radioactive decontamination) from an object or surface must be balanced with the risk of spreading radioactive contamination. At times the best approach may be to shield the area until the radiation exposure levels are lower. This balance must be specified in SOPs (e.g., trigger levels for safe cleaning). The PEC should be checked for radioactive contamination prior to cleaning and disinfecting to prevent spreading radioactive contamination in the PEC.

All cleaning and disinfecting activities must be performed by trained and appropriately garbed personnel using facility-approved agents and procedures that must be described in written SOPs. Cleaning must be performed in the direction of most to least clean areas. The frequency, method(s), and location(s) of cleaning, disinfecting, and sporicidal agent use must be established in written SOPs, in accordance with the manufacturer's instructions when available, or based on sound microbiological cleaning techniques when unavailable, and must be followed by all cleaning personnel. The manufacturer's

direction or published data for the minimum contact time must be followed for the cleaning, disinfecting, and sporicidal agents used. When sterile 70% IPA is used, it must be allowed to dry. All cleaning, disinfecting, and application of sporicidal agents must be documented according to facility SOPs.

Table 5. Minimum Frequency for Cleaning and Disinfecting Surfaces in Classified Areas and within the Perimeter of the SRPA

Site	Cleaning	Disinfecting[a]	Applying Sporicidal
PEC(s) and equipment inside the PEC(s)	Prior to performing sterile processing of radiopharmaceuticals on each day that activities are carried out, the walls, bars, torso shield and any exposed surface of equipment inside the PEC must be cleaned to the extent possible as specified by the equipment manufacturer or the assessment of a qualified individual (e.g., microbiologist or industrial hygienist). Radioactive contamination may be shielded with appropriate temporary material, providing the material is covered with low-lint absorbent pads or has equivalent low-shedding properties.	Following cleaning on each day that activities are carried out, exposed surfaces of the equipment should be disinfected to the extent possible as specified by the equipment manufacturer or the assessment of a qualified individual (e.g., microbiologist or industrial hygienist). When used, remove low-lint absorbent pads and survey the PEC for radioactive contamination prior to disinfecting. Replace with new pads after disinfecting or as required after spills.	Monthly
Surfaces of sink(s)	Daily	Daily	Monthly
Hot-cells (all interior surfaces, dependent on design, equipment, and shielding present)	Daily	Daily	Monthly
PEC and the equipment inside the PEC(s) located in a hot-cell	Prior to performing sterile processing of radiopharmaceuticals on each day that activities are carried out, the walls, bars, torso shield, and any exposed surface of equipment inside the PEC to the extent possible as specified by the equipment manufacturer or the assessment of a qualified individual (e.g., microbiologist or industrial hygienist). Radioactive contamination may be temporarily shielded with appropriate temporary material providing the material is covered with low-lint absorbent pads or has equivalent low-shedding properties.	Following cleaning on each day that activities are carried out, exposed surfaces of the equipment should be disinfected to the extent possible as specified by the equipment manufacturer or the assessment of a qualified individual (e.g., microbiologist or industrial hygienist) and should be specified by SOPs. Remove low-lint absorbent pads and survey the PEC for radioactive contamination prior to disinfecting. Replace with new pads after disinfecting or as required after spills.	Monthly
Work surface(s) outside the PEC	Daily	Daily	Monthly
Ceiling(s)	Monthly	Monthly	Monthly
Wall(s), door(s), door frame(s), and other fixtures	Monthly	Monthly	Monthly
Floor(s)	Daily	Daily	Monthly
Storage shelving and storage bins	Monthly	Monthly	Monthly

[a] Many disinfectants registered with the EPA are one-step cleaning and disinfecting agents, which means that the disinfectant has been formulated to be effective in the presence of light to moderate soiling without a separate cleaning step. Cleaning and disinfecting must be balanced with the risk of spreading radiation contamination. The best approach may be to shield the area until the radiation exposure levels are lower.

7.1 Cleaning, Disinfecting, and Sporicidal Agents

Cleaning and disinfecting agents must be selected and used with careful consideration of compatibilities, effectiveness, and user safety. Considerations when selecting and using disinfectants include their anti-microbial activity, inactivation by organic matter, residue, shelf life, preparation requirements of the agent, and suitability for surfaces being disinfected (see *Disinfectants and Antiseptics* ⟨1072⟩). After the disinfectant is applied on the surface to be disinfected, the disinfectant must be allowed to dwell for the minimum contact time specified by the manufacturer, during which time the surface cannot be disturbed. Only the 70% IPA used in the ISO Class 5 PEC must be sterile. Sporicidal agents must be used at least monthly on all surfaces in classified areas and SRPAs. Some EPA-registered (or equivalent) one-step disinfectant cleaners may have sporicidal properties. See *Table 6* for a summary of the purpose of the cleaning, disinfecting, and sporicidal agents.

Table 6. Purpose of Cleaning, Disinfecting, and Sporicidal Agents

Type of Agent	Purpose
Cleaning agent	An agent for the removal of residues (e.g., dirt, debris, microbes, and residual drugs or chemicals) from surfaces.
Disinfecting agent	A chemical or physical agent used on inanimate surfaces and objects to destroy fungi, viruses, and bacteria.
Sporicidal agent	A chemical or physical agent that destroys bacterial and fungal spores when used in sufficient concentration for a specified contact time. It is expected to kill all vegetative microorganisms.

7.2 Cleaning Supplies

All cleaning supplies (e.g., wipers and mop heads), with the exception of tool handles and holders, must be low-lint and should be disposable. If disposable cleaning supplies are used, they must be discarded after each cleaning activity. Reusable cleaning tools must be made of cleanable materials (e.g., no wooden handles) and must be cleaned and disinfected before and after each use. Reusable cleaning tools must be dedicated for use in the classified areas or SRPAs and must not be removed from these areas except for disposal. They must be discarded after an appropriate amount of time, to be determined based on the condition of the tools. Cleaning supplies and solutions used in the classified areas and SRPAs should be monitored for radioactive contamination after use and prior to disposal, as per facility SOPs. Dispose of cleaning supplies used in the classified areas and SRPAs in a manner that minimizes the potential for dispersing particulates into the air (e.g., with minimal agitation, away from work surfaces).

7.3 Cleaning and Disinfecting the PEC

Clean and disinfect the PEC at the minimum frequencies specified in *Table 5*. If the PEC contains a removable work tray, all sides of the work tray and the area underneath the work tray must be cleaned and disinfected at least monthly.

1. Survey all surfaces of the PEC for radioactive contamination and follow facility SOPs to decontaminate, if necessary.
2. Remove, if necessary, any particles, debris, or residue with an appropriate solution (e.g., *Sterile Water for Injection* or *Sterile Water for Irrigation*) using sterile, low-lint wipers.
3. Apply a cleaning agent followed by a disinfecting agent or apply an EPA-registered (or equivalent) one-step disinfectant cleaner and ensure that the contact time specified per manufacturer instructions is achieved.
4. Apply sterile 70% IPA
5. Allow the surface to dry completely before beginning activities.
6. The PEC must be wiped with a sporicidal agent at least monthly.

7.4 Disinfecting Supplies for Classified Areas and SRPAs

No shipping carton(s) or other corrugated or uncoated cardboard are allowed in the classified area (e.g., clean side of ante-room) or within the perimeter of the SRPA. Before items are introduced into a classified area or SRPA, they must be wiped with a sporicidal agent, EPA-registered (or equivalent) one-step disinfectant cleaner, or sterile 70% IPA using low-lint wipers. After the sporicidal or sterile disinfectant is applied onto the surface, the agent must be allowed to dwell on the surface for the minimum contact time specified by the manufacturer (see *6.1 General Monitoring Requirements*). The agent used for disinfecting the packaging must be compatible with the packaging and must not render the product label unreadable.

Any item to be transferred into the PEC from the classified area or SRPA must be disinfected with a sterile disinfectant (e.g., sterile 70% IPA).

In the case of radiopharmaceuticals being processed by remote means in a hot-cell, the opening of sterile packages (e.g., syringes, luer lock caps) may not be possible by remote means within the ISO Class 5 area. In this case, the syringes may be opened and appropriately labeled outside of the ISO Class 5 environment and placed in disinfected shielding, immediately prior to the forthcoming dispensing cycle.

7.5 Disinfecting Critical Sites

Critical sites (e.g., vial stoppers) must be wiped with sterile 70% IPA. The critical site must be wiped ensuring that both chemical and mechanical actions are used to remove contaminants. The sterile 70% IPA must be allowed to dry before piercing critical sites.

7.6 Cleaning and Disinfecting Items from Patient Care Area

Radiation shielding and equipment used in the classified area/SRPA or PEC that is exposed to patient care areas during the process of administration must be cleaned and disinfected before returning to any classified area (e.g., buffer or ante-room) or SRPA in accordance with the Centers for Disease Control and Prevention guidelines[1] as noncritical equipment requiring low-risk disinfection. Syringes that have been used in a patient care area must not be brought back into the classified area (e.g., buffer or ante-room) or SRPA for re-assaying or disposal unless the syringe is sealed inside an impervious container (e.g., sealed plastic bag) that is disinfected prior to entry into the classified area or SRPA. Equipment that has been exposed to needles and syringes contaminated with blood-borne pathogens and RAMs are considered mixed waste (e.g., syringe shields and syringe carrying containers). This equipment must be cleaned and disinfected through actions regulated by the facilities' SOPs. Equipment that contained or was in contact with mixed waste must be cleaned and disinfected with an appropriate agent(s) for blood.

8. ASSIGNING BUD

BUDs are based on the risk of microbial contamination with the assumption that the radiopharmaceutical(s) should remain chemically and physically stable, and its container–closure system should maintain its integrity for the duration of the BUD (*Table 7*). The time starts at the moment of the first sterile vial puncture or exposure of a critical site (e.g., syringe tip, needle hub, or needle) to ambient air, whichever is first. The BUDs stated in *Table 7* are maximum values in the absence of sterility

[1] Centers for Disease Control and Prevention. *Guideline for Disinfection and Sterilization in Healthcare Facilities*, 2008.

testing, and the assigned BUD may be shorter for a variety of reasons discussed below. The individual responsible for the manipulation assigns the BUD based on established testing data, either performed in-house or obtained from peer-reviewed literature.

Table 7. Preparation Conditions for Sterile Radiopharmaceuticals

Preparation Conditions			
Manipulation	**PEC**	**SEC**	**BUD (hours)**
Immediate use	—	—	1
Direct infusion system, one puncture only (e.g., PET patient infusion system, Rb-82 generator)	—	—	10
Dispensing, repackaging, preparation, and preparation with minor deviations	ISO Class 5	SRPA	12
Radionuclide generator storage/elution (e.g., non-direct infusion system; Tc-99m or Ga-68)	—	SRPA with ISO Class 8 total airborne particle count	12
Radionuclide generator storage/elution (e.g., non-direct infusion system; Tc-99m or Ga-68)	—	ISO Class 8 or better buffer area with ISO Class 8 or better ante-room	24
Dispensing, repackaging, preparation, and preparation with minor deviations	ISO Class 5	ISO Class 8 or better buffer area with ISO Class 8 or better ante-room	24
Dispensing, repackaging, preparation, preparation with minor deviations, and compounding using sterile components	ISO Class 5	ISO Class 7 or better buffer area with ISO Class 8 or better ante-room	96
Dispensing, repackaging, preparation, preparation with minor deviations, and compounding using a nonsterile component and performing sterilization procedure (e.g., filtration with bubble point testing) but without performing *Sterility Tests* ⟨71⟩ testing	ISO Class 5	ISO Class 7 or better buffer area with ISO Class 8 or better ante-room	24
Radiolabeled blood components for immediate use [e.g., Tc 99m red blood cells (RBC)]	—	—	1
Radiolabeled blood components (e.g., radiolabeled leukocytes)	ISO Class 5 BSC	ISO Class 7 or better buffer area with ISO Class 8 or better ante-room	6 h after the blood sample is obtained

For compounded preparations (sterile and nonsterile), the BUD is also dependent on maintenance of appropriate quality and purity, including radiochemical purity, radionuclidic purity, and other applicable parameters as specified in individual monographs or as clinically appropriate.

For preparations with minor deviations involving conventionally manufactured kits (sterile and nonsterile), the kit may state or suggest a use-by time in the package insert. For certain radiopharmaceuticals transportation time, radionuclide availability, and other factors may necessitate extending manufacturer-stated/suggested use-by time to meet patient needs. Assigning a BUD longer than the manufacturer-stated/suggested use-by time interval must be supported by evidence of the maintenance of appropriate quality and purity, including radiochemical purity and radionuclidic purity as specified in individual monographs, and other applicable parameters as clinically appropriate.

Assignment of a BUD for a radiopharmaceutical(s) must consider several factors, as applicable. Issues of concern include, but are not limited to, the following:

- Sterility: Maintenance of sterility is a major concern for any sterile preparation or product. Good aseptic handling practices in an appropriate environmentally-controlled area are the most critical factors in ensuring sterility. See *Table 7* for maximum BUD. The assigned BUD should not exceed the sterility-related times listed in *Table 7*, unless a longer time is justified by *Sterility Tests* ⟨71⟩.
- Radiochemical purity: Maintenance of radiochemical purity is affected by a variety of factors including, but not limited to, storage temperature, quantity of radioactivity, radioactivity concentration, presence or absence of antioxidants or other stabilizing agents, and container type (e.g., glass vial vs. plastic syringe). The assigned BUD must be based on stability studies in which these variables are controlled and are representative of the conditions of actual use. For factors that allow a range of values (e.g., storage temperature, quantity of radioactivity, radioactivity concentration), studies should be conducted at the extremes of the ranges.
- Radionuclidic purity: Because radionuclidic impurities may decay away more slowly than the primary radionuclide, the radionuclidic purity may decrease over time. For example, the ratio of Mo-99 (half-life of about 66 hours) to Tc-99m (half-life of about 6 hours) continuously increases over time. *USP* monographs for Tc-99m radiopharmaceuticals require that the radionuclidic impurity Mo-99 not exceed 0.15 μCi Mo-99 per mCi Tc-99m at the time of administration. Calculation of radionuclidic purity at future times is necessary to ensure compliance throughout the assigned BUD.

- Age of generator eluate: As a generator eluate decays, the desired daughter radionuclide decays to form other nuclides and potential radiolytic products, which may interfere with radiolabeling of kits. For example, Tc-99m undergoes decay to Tc-99. More importantly, increasing amounts of peroxides formed as radiation interacts with water molecules. Increased amounts of Tc-99 and peroxides can interfere with the radiolabeling of many kits. Extension of the BUD for Tc-99m pertechnetate intended for radiolabeling of kits must take into account the build-up of Tc-99 and peroxides over time.
- Number of particles: For radiolabeled particulates, the number of particles per unit radioactivity increases over time as the radionuclide decays. For example, the BUD for Tc-99m albumin aggregated [macroaggregated albumin (MAA)] must take into account the increasing ratio over time of the number of particles per unit radioactivity. For example, if an MAA kit is prepared such that the radioactive patient dose is 200,000 particles at the time of calibration, the same patient dose will contain 700,000 particles at 10.85 hours after calibration. Calculation of the number of MAA particles in the patient dose is necessary to ensure compliance with the prescribed particle range throughout the assigned BUD.
- Specific activity: For some receptor-based radiopharmaceuticals, the mass quantity may influence uptake (i.e., too much mass may result in saturation of receptor sites and reduce target uptake of the radiopharmaceutical). As radioactivity decays over time, specific activity decreases resulting in more mass per unit radioactivity. In such situations, the assigned BUD must ensure that the patient dose contains no more than the specified maximum mass.
- Container type: Because radiochemical stability or other quality attributes of a radiopharmaceutical may be affected by its container characteristics, the BUD for a radiopharmaceutical dose dispensed in a plastic syringe may be different than the BUD of that same radiopharmaceutical maintained in a glass vial. The assigned BUD must be determined in the proper storage container.
- Cell viability: The viability of radiolabeled blood cells (e.g., leukocytes) decreases over time, and may also be affected by other factors such as the suspending medium, temperature, and agitation. The assigned BUD should be as short as circumstances reasonably allow so as to maximize cell viability.
- In the case of manufactured radiopharmaceuticals that are distributed to nuclear pharmacies or other healthcare facilities for terminal distribution/dispensing, the assigned BUD of the dispensed dose cannot exceed the expiration date/time of the manufactured radiopharmaceutical(s).
- In the case of radiopharmaceuticals prepared from kits, the BUD of a dispensed dose cannot exceed the assigned BUD of the finished kit preparation.
- A radiopharmaceutical may not exceed the shortest BUD of any of its components.

The facility must have policies and SOPs appropriate to the assignment of BUD and maintain documentation of applicable study results and calculations. Studies of radiolabeling efficiency and radiochemical stability should employ quality control (QC) testing methods described in the manufacturer's package insert, *USP* monographs and general chapters, or other equivalent testing methods and be sufficiently rigorous to allow statistical confidence in the results.

The facility must have SOPs to collect and evaluate complaints associated with the use of radiopharmaceuticals having assigned BUDs. Policies and SOPs should also be in place to reevaluate the assigned BUD based on complaints, which may include repeating studies and/or performing additional studies on radiolabeling efficiency and/or radiochemical stability.

9. DOCUMENTATION

Applicable records (hard-copy or electronic), including policies and SOPs, must be maintained for all activities involved in repackaging, preparing, preparing with minor deviations, compounding, and dispensing radiopharmaceuticals. Such records include, but are not limited to:

- Personnel training and testing, including visual assessment of aseptic technique competency, validation, garbing, hand hygiene, equipment/environment cleaning and disinfecting, gloved fingertip and thumb sampling, and media fill evaluation initially and follow up testing at specified intervals.
- Testing and monitoring of environmental controls, including ISO classification, ACPH, pressure differentials, temperature, humidity and viable air/surface and total airborne particle test results
- Equipment maintenance and cleaning/disinfecting
- End product radiochemical purity and other testing, as applicable, results of preparations, preparations with minor deviations, and compounded preparations
- Master Formulation Record (MFR) for preparation with minor deviation(s) and compounding
- Validation of stability testing to support the assigned BUD from SOPs by the compounder or derived from accepted literature
- Investigations and corrective actions and tracking of events to closure.

9.1 Master Formulation Record

A MFR is required only for a preparation with minor deviations or compounding, as described in *11. Compounding*. A MFR is not required for a preparation following the manufacturer's instructions.

Data that must be included in the MFR are as follows:

- Name of the radiopharmaceutical
- Name, identity, strength, purity, quality, and quantity of ingredients with validated documentation (e.g., CoA)
- Detailed procedure (e.g., heating, components, incubation time)
- Range of radioactivity
- Range of volume
- Equipment to be used

- PEC and SEC to be used, if applicable
- Quality control tests to be performed for final release of the radiopharmaceutical (e.g., radiochemical purity, pH)
- Procedures for depyrogenation and sterility procedures and validations, as applicable, including limits
- Trained personnel
- Garbing procedure, if different than standard procedure
- Container(s)
- Reference source of the BUD assignment and storage conditions

9.2 Records for Preparation with Minor Deviations/Compounding

A record for preparation with minor deviation or compounding must include the following:

- Name of the radiopharmaceutical
- Physical form (e.g., capsule or solution)
- Name and quantity of ingredients including calibration time for radioactive ingredients (e.g., 100 mCi Tc 99m sodium pertechnetate @ 1300)
- Total volume
- Reference to the MFR
- Any deviation from the MFR, if applicable
- Name of vendor or manufacturer, lot numbers, and expiration dates of all ingredients and components
- Name of the person who prepared and name of the supervising personnel (e.g., ANP or AU physician)
- Date and time of preparation
- Assigned internal identification number (e.g., lot number)
- Unique reference [e.g., prescription, order number(s)]
- Assigned BUD and storage requirements
- Documentation of QC results

10. PREPARATION

The individual responsible for preparing the radiopharmaceutical(s) must ensure that the final preparation complies with quality and purity specifications throughout the assigned BUD. This includes, as appropriate for the preparation, radionuclidic purity, radiochemical purity, chemical purity, and physical and chemical properties.

10.1 Preparation Following Manufacturer Instructions

NONSTERILE PREPARATIONS

For nonsterile preparations, follow manufacturer preparation instructions (e.g., I-131 NaI capsules or solution), taking into account appropriate radiation safety considerations and environmental controls, if applicable (e.g., negative air pressure area, chemical fume hood, activated charcoal filters when handling a potentially volatile radionuclide). The area should be suitably cleaned and uncluttered to ensure the overall integrity and quality of the prepared radiopharmaceutical(s). There should be a documented process for activities (e.g., cleaning) between the preparation cycles of different nonsterile products, to decrease the likelihood of contamination from other prepared products.

STERILE PREPARATIONS

For sterile preparations (including intravascular devices), follow manufacturer preparation instructions, taking into account appropriate radiation safety considerations, appropriate environmental controls, and aseptic handling practices to maintain sterility. The minimum environmental standard for the preparation of sterile radiopharmaceuticals beyond immediate-use is within an ISO Classified area or device (see *Table 7*). Refer to *5. Facilities and Environmental Controls* and *Table 7* on the location of the PEC and the assignment of the BUD.

10.2 Preparation with Minor Deviations

In some cases, radiopharmaceuticals are prepared with minor deviations from manufacturer instructions that are necessary to accommodate circumstances not contemplated in the FDA-approved labeling. Note that *General Notices, 5.20.20.1 In Compounded Preparations* includes the statement: "Deviation from the specified processes or methods of compounding, although not from the ingredients or proportions thereof, may occur provided that the finished preparation conforms to the relevant standards and to preparations produced by following the specified process." However, except for a few receptor-based radiopharmaceuticals where specific activity is an important parameter, there is a very broad range of acceptable values for specific activity and for proportions of ingredients. Deviations from manufacturer preparation instructions for radiopharmaceuticals must maintain the same ingredients but may differ in their proportions.

This requires appropriate in-house QC testing, designed to validate the radiochemical purity of the product for the entirety of the BUD or is supported by appropriate peer-reviewed publications for the minor deviation utilized.

Examples of minor deviations include, but are not limited to, the following:

- Altering the quantity of radioactivity or volume added to the vial
- Changes in step-by-step operations (e.g., dilute Tc-99m sodium pertechnetate after rather than before addition to the vial)
- Using alternative devices or equipment (e.g., a heating block rather than a hot water bath, using a different sized needle, different shielding materials)
- Using QC test methods other than those described in the product labeling (e.g., radiochemical purity)
- Filtering Tc-99m sulfur colloid

10.3 Preparation of Radiolabeled Blood Components

Handling blood and radiolabeling of blood components requires special attention to biological risks and must be handled with standard precautions using aseptic technique to prevent the introduction of new microorganisms into the preparation that will be administered. Due to the potential presence of microorganisms in the original blood sample, the preparation must be administered as soon as possible but no later than 6 hours after the blood sample is obtained from the patient or blood bank.

The presence of microorganisms in a blood sample may present a risk to the individual performing the preparation as well as cross-contamination to other blood samples or other non-blood related radiopharmaceuticals. Equipment and supplies should never be shared with other activities unless they are first thoroughly cleaned and disinfected. Special precautions when radiolabeling of blood components for non-immediate use include:

- There must be complete physical separation (either fixed or non-fixed wall) of areas where blood products are handled from areas where non-blood products are handled. An ISO Class 5 BSC located in an ISO Class 7 buffer area is required for blood-labeling processes. If more than one ISO Class 5 PEC is located within the ISO Class 7 buffer area, policies and SOPs must be in place to include certification that the SEC meets conditions of air quality at maximum occupancy under dynamic operating conditions.
- One radiolabeling procedure per PEC at a time. Blood products from more than one patient must never be manipulated at the same workstation at the same time. Each area should have dedicated supplies, equipment (including dose calibrator), and waste disposal to eliminate sharing of these items or overlap in pathways.
- Thorough cleaning and disinfection of the ISO Class 5 BSC and all reusable equipment within, prior to starting another blood component radiolabeling procedure.
- If a dedicated dose calibrator is not available, then a means of preventing the blood container(s) from contaminating the dose calibrator must be used or the dose calibrator dipper and liner must be cleaned and disinfected following the radioassay.
- Centrifuge should be located within the ISO Class 7 buffer area that is dedicated for blood component radiolabeling processes.
- Dedicated (per each radiolabeling procedure) consumable products (e.g., 0.9% sodium chloride injection, diluent, tubes, syringes, and other supplies) necessary for each individual patient radiolabeling procedure.
- All tubes and syringes in contact with the patient's blood components must be clearly labeled with the patient's name and at least one additional identifier (e.g., date of birth, medical record number, barcode).
- Dedicated syringe shields and vial shields.
- Remove and replace any garb that enters the ISO Class 5 BSC before handling anything else not related to performing this procedure.
- Removal of all disposable items from the ISO Class 5 BSC utilized in each radiolabeling procedure.
- Cleaning and disinfection of all reusable equipment and components (e.g., BSC, centrifuge, dose calibrator, syringe shields, vial shields, syringe transport shields and delivery cases) after each radiolabeling procedure prior to any further use. Policies and SOPs must address cleaning and disinfection processes including the use of an EPA-registered (or equivalent) one-step disinfectant cleaner with activity against blood-borne pathogens followed by sterile 70% IPA. Sterile 70% IPA alone is not sufficient.
- After the completion of blood radiolabeling procedures, follow all requirements in *4.5 Hand Hygiene and Garbing for Buffer Areas and segregated Radiopharmaceutical Processing Area*.

10.4 Preparation of Radiolabeled Red Blood Cells for Immediate Use

In vitro red blood cell labeling must be prepared while following the conditions below:

- A dedicated space for blood handling must be designated through the entirety of the blood radiolabeling process. This area must be free from clutter and not used for any other radiopharmaceutical preparation or handling until the completion of cleaning and disinfection.
- Perform only one radiolabeling procedure at a time or have documented processes that maintain the integrity of samples and environment.
- Dedicated equipment must be used for blood radiolabeling procedure (e.g., L-block, syringe shield, vial shield, forceps, needle recapper).
- If a dedicated dose calibrator is not available, then a means of preventing the blood container(s) from contaminating the dose calibrator or a cleaning and disinfecting procedure with an appropriate product must be used to decontaminate the dipper and liner of the dose calibrator following the radioassay
- A cleaning and disinfecting procedure with an appropriate agent(s) must be used to decontaminate the area and equipment prior to and after the radiolabeling is complete and all disposable components have been discarded
- Follow all requirements in *4.4 Hand Hygiene and Garbing for Immediate Use Preparations*.

- The start time of the preparation must begin with the initial container puncture or the exposure of a critical site (e.g., syringe tip, needle hub or needle) to ambient air, whichever is first.
- BUD of 1 hour (see *Table 7*).

11. COMPOUNDING

Each compounding activity must be based on a pre-established written procedure and must include maintenance of compounding records. The compounding record must provide traceability (see *9. Documentation*).

All sterile compounding, using aseptic technique, must be performed in an ISO 5 PEC. Refer to *5.7 Environmental Controls* and *Table 7* for further clarification on the location of the PEC and the applicability of the radiopharmaceutical BUD.

Compounding must not be performed for any radiopharmaceutical(s) that has been withdrawn from the market because of safety or lack of effectiveness, unless part of an institutional review board approved investigational study. Radiopharmaceuticals that are essentially copies of marketed FDA-approved radiopharmaceuticals must not be compounded unless there is a change that produces a clinical difference for an identified individual patient, as determined by a prescriber.

11.1 Compounding Nonsterile Radiopharmaceuticals

Compounding nonsterile radiopharmaceuticals is the combining, mixing, diluting, pooling, reconstituting or otherwise altering a drug or bulk drug substance other than as provided by the manufacturer's package insert to create a nonsterile radiopharmaceutical. Examples of compounding nonsterile radiopharmaceuticals include: changing the dosage form of a capsule to a solution, changing an intravenous dosage form to an oral dosage form, and radiolabeling a food for oral administration (e.g., Tc-99m sulfur colloid in eggs). Areas designated for nonsterile compounding must be cleaned and uncluttered and separated from areas designated for sterile radiopharmaceuticals. Compounding should take into account RAM licensing requirements for appropriate radiation safety considerations and utilize appropriate environmental controls, if applicable (e.g., chemical fume hood, activated charcoal filters when handling potentially volatile radionuclides). The placement of equipment and materials must take into account a design that prevents cross-contamination.

When feasible, disposable material should be used to reduce the chance of cross-contamination. Each compound must have a unique MFR (see *9.1 Master Formulation Record*). The preparation information is documented on a compounding record (see *9.2 Records for Preparation with Minor Deviations/Compounding*). The MFR details the selection of all components. The ingredients must be obtained from sources in this preferential order: FDA-approved product; FDA-registered facility; and lastly, if the ingredients for the compound are not available from either of these two sources, the MFR must detail the selection of a material that is suitable for the intended use. The MFR must establish the identity, strength, purity, and quality of the ingredients by validated means (e.g., CoA). Requirements for nonsterile oral meal components are limited to common food grade description and are not required to establish identity by validated means.

A BUD for the compounded radiopharmaceutical must be validated, taking into account the stability of the ingredients, any intermediate containers, the final container, and the storage conditions. A BUD cannot be extended past the labeled expiration date of any component in the compound. If the compounded radiopharmaceutical(s) includes components from other preparations or preparations with minor deviations, the BUD of the final compounded radiopharmaceutical must not exceed the shortest remaining BUD of any of those components.

11.2 Sterile Compounding

Some compounding activities involve only the addition of a conventionally manufactured drug product (e.g., *Ascorbic Acid Injection*, *Lidocaine Hydrochloride Injection*, *Sodium Bicarbonate Injection*) approved by the appropriate regulatory agency to a radiopharmaceutical.

Personnel responsible for compounding must consider all possible interactions between the components, such as altered chemical stability, radiochemical stability, solubility, or other parameters (e.g., osmolality) related to changes in pH, excipients, or other factors, in determining an appropriate BUD. In some cases, this may require systematic QC testing over time to validate the appropriateness of a particular BUD.

Another activity that is considered a compounding activity is the splitting of conventionally marketed kits. Kit-splitting (also referred to as "fractionation") may be used to meet patient need. For example, the contents of a kit vial can be reconstituted with 0.9% sodium chloride injection and aliquoted into other containers for storage and subsequent radiolabeling. The individual responsible must consider all possible interactions of kit components with these other containers (e.g., container walls, closures), as well as possible alterations in stability (e.g., physical stability, chemical stability) that may affect radiolabeling yields or performance parameters, when determining an appropriate BUD. Systematic QC testing is required to validate the appropriateness of a particular BUD.

11.3 Sterile Compounding Using a Nonsterile Drug Substance or Components

Some sterile compounding activities involve the use of materials other than commercially marketed products, such as drug substances and/or radionuclides. If one or more materials or components are not certified to be sterile and pyrogen-free, a sterilization procedure (e.g., filtration with bubble point testing) and testing described in ⟨85⟩ must be performed. The designated person for compounding is responsible for ensuring that the final preparation complies with pre-established standards or acceptance criteria for identity, quality, and purity, and must consider all possible interactions between the components, such as altered chemical stability, radiochemical stability, solubility, or other parameters (e.g., osmolality) related to changes in pH, excipients, or other factors, in determining an appropriate BUD. This may require testing to validate the appropriateness of a particular BUD.

If compounding involves a bulk drug substance, the radiopharmaceutical must comply with standards of an applicable *USP* or *NF* monograph, if one exists, or be a component of an approved drug product. For this chapter, a bulk drug substance includes a radionuclide, a ligand, or other substance, such as a precursor that becomes an active ingredient in the final radiopharmaceutical. Each bulk drug substance should be manufactured by drug establishments registered with FDA and be accompanied by a valid CoA or equivalent testing procedures.

If compounding involves excipients or other inactive ingredients, the excipients or other inactive ingredients must comply with standards of an applicable *USP* or *NF* monograph, if one exists. It is also acceptable that any excipients or other inactive ingredients be approved products, manufactured by a drug establishment registered with the FDA.

12. DISPENSING

12.1 Dispensing and Radioassay

Dispensing refers to the manipulations necessary to transfer the prescribed or ordered amount of radiopharmaceutical into the final container (e.g., syringe or vial). Dispensing can take place from single-dose or multiple-dose containers of prepared, prepared with minor deviations, compounded, or manufactured radiopharmaceuticals, and may involve needle changes, affixing a sterile cap, or dilution (e.g., adding 0.9% sodium chloride injection) in the final container. For nonsterile radiopharmaceuticals, an example is obtaining 1 capsule from a container holding 1 or more capsules. For sterile radiopharmaceuticals, an example is withdrawing a volume of solution from a single-use or multiple-dose container into a syringe. Labeling of the final patient-ready dose or ordered amount of a radiopharmaceutical is also a component of the dispensing process.

Except for an unopened manufacturer container, the final dose or ordered amount must be radioassayed (i.e., in a dose calibrator). The measured activity should be mathematically corrected for radioactive decay to the time of scheduled administration (calibration time) (refer to *14. Quality Assurance and Quality Control*). The activity at calibration time must always be within federal, state, and local variance limits.

12.2 Labeling

The labeling of radiopharmaceuticals can fall under the jurisdiction of numerous regulatory agencies. Individual boards of pharmacy and other regulatory bodies may have very specific statutes and/or regulations concerning this process. The requirements specified in this chapter must be considered the minimum requirements for the labeling of the inner container (e.g., syringe, vial) and the outer shielding (e.g., syringe or vial shielding). Therefore, all personnel distributing and/or dispensing radiopharmaceuticals should verify that any labeling is in compliance with regulatory agencies.

The inner container must be labeled with the following:

- Standard radiation symbol
- The words “Caution—Radioactive Material”
- For all therapeutic and blood-products, the patient name/identifier
- Radionuclide and chemical form (generic name)
- Radioactivity at the date and time of calibration

The outer shielding must be labeled with the following:

- Standard radiation symbol
- The words “Caution—Radioactive Material”
- For all therapeutic and blood-products, the patient name/identifier
- Radionuclide and chemical form (generic name)
- Radioactivity at the date and time of calibration
- Volume or number of units dispensed (e.g., 2 capsules), as applicable
- Product expiration or BUD (see *Table 7*), as applicable, and any special storage and handling instructions for non-immediate use (e.g., refrigeration, resuspension)
- Route of administration

12.3 Direct Infusion Systems

The information in this section is limited to the sterility and aseptic technique for direct infusion systems. The described infusion systems are FDA-cleared medical devices or FDA-approved direct infusion generators without an ISO-5 environment. The manner in which all necessary solutions (e.g., radiopharmaceutical and eluant/diluent) are used in conjunction with the system was a consideration in the overall approval process for the system. Therefore, all operators of the direct infusion systems must follow the “Instructions for Use” in the device labeling.

- Direct infusion generators (e.g., rubidium chloride Rb 82 injection) may employ a container of eluant (e.g., bag of 0.9% sodium chloride injection) to allow administration of the eluate directly to patient(s).
- Direct infusion devices (e.g., portable PET patient-infusion system) provide a method for dispensing and administration from a multiple-dose container of the radiopharmaceutical (e.g., fludeoxyglucose F 18 injection) and the diluent (e.g., 0.9% sodium chloride injection) directly to patients to reduce the radiation exposure to personnel.

In each of these situations, the radiopharmaceutical container must be attached to or be needle-punctured by the respective direct infusion system. Given that such direct infusion systems are intended for multiple patients over the course of several

hours, there could be a sterility concern if not operated properly. Therefore, the following parameters must be considered by the operator of the system:

- Setup attachment or needle-puncture should be performed in a defined environment
- Aseptic handling in ambient air with a maximum BUD of 10 hours is allowed for these direct infusion systems (see *Table 7*)
- The 0.9% sodium chloride bag attached to the device may only be punctured once and may be used for no more than 10 hours. The bag must be labeled with the date and time of puncture and the BUD
- Any nonsterile parts of the device that may encounter the septum of the radiopharmaceutical vial must be disinfected with sterile 70% IPA prior to puncturing the vial with the needle
- The septum of any vial and the ports of any diluent bag must be wiped with sterile 70% IPA prior to puncturing
- When puncturing the vial in ambient air, it must only be punctured once
- If there are problems with the infusion device, no sterile container(s) associated with the system can be repunctured or transferred to a PEC for further manipulations and the container, with contents, must be discarded

12.4 Transporting Generators Between Facilities

The following standards must be followed if transporting generators between facilities:

- The generator needle and/or ports must be capped in ISO Class 8 air or better with sterile protectors
- The generator must be packaged and transported in a manner to maintain the integrity and sterility of the generator system

13. REPACKAGING

Repackaging refers to the act of removing conventionally manufactured radiopharmaceutical(s) from the container in which it was distributed by the original manufacturer and placing it into a different container without further manipulation of the product. Repackaging also includes the act of placing the contents of multiple containers of the same finished drug product into one container, as long as the container does not include other ingredients. Repackaging may be performed for nonsterile radiopharmaceuticals (e.g., I-131 sodium iodide oral capsules) and for sterile radiopharmaceuticals (e.g., thallous chloride Tl 201 injection).

Except for unopened manufacturer dosage units (e.g., capsules, Xe-133 vials), the repackaged radiopharmaceutical must be radioassayed (i.e., in a dose calibrator). The inner container should be labeled with the following:

- Standard radiation symbol
- The words “Caution—Radioactive Material”
- The radionuclide and chemical form (generic name)
- Radioactivity with units at time of calibration and the calibration time

The outer shielding should be labeled with the following:

- Standard radiation symbol
- The words “Caution—Radioactive Material”
- The radionuclide and chemical form (generic name)
- Radioactivity with units at time of calibration and the calibration time
- Volume, or number of units (e.g., capsules), as applicable
- Product expiration or BUD (see *Table 7*), as applicable
- Special storage and handling instructions

14. QUALITY ASSURANCE AND QUALITY CONTROL

Quality assurance (QA) is a system of procedures, activities, and oversight that ensures that radiopharmaceutical processing consistently meets quality standards (see *Quality Assurance in Pharmaceutical Compounding* ⟨1163⟩). Quality control (QC) is the sampling, testing, and documentation of results that, taken together, ensure that specifications have been met before release of the radiopharmaceutical(s).

A facility’s QA and QC programs must be formally established and documented in SOPs that ensure that all aspects of the handling of radiopharmaceuticals are conducted in accordance with this chapter and applicable federal, state, and local laws and regulations. A designated person must ensure that the facility has formal, written QA and QC programs that establish a system of:

1. Adherence to procedures,
2. Prevention and detection of errors and other quality problems,
3. Evaluation of complaints and adverse events, and
4. Appropriate investigations and corrective actions.

The SOPs must describe the roles, duties, and training of the personnel responsible for each aspect of the QA program. The overall QA and QC program must be reviewed at least once every 12 months by the designated person. The results of the review must be documented and appropriate corrective action taken, if needed.

14.1 Notification About and Recall of Out-of-Specification Dispensed Radiopharmaceuticals

If a radiopharmaceutical is dispensed or administered before the results of release testing are known, the facility must have SOPs in place to:

1. Immediately notify the prescriber of a failure of specifications with the potential to cause patient harm (e.g., sterility, strength, purity, bacterial endotoxin, or other quality attributes), and
2. Determine whether a recall is necessary.

The SOP for recall of out-of-specification dispensed radiopharmaceuticals must contain procedures to:

- Determine the severity of the problem and the urgency for the implementation and completion of the recall
- Determine the distribution of any affected radiopharmaceutical, including the date and quantity
- Identify patients who have received the radiopharmaceutical
- Outline the disposition and reconciliation of the recalled radiopharmaceutical

The facility must document the implementation of the recall procedures. The recall must be reported to appropriate regulatory bodies as required by laws and regulations of the applicable regulatory jurisdiction (e.g., state board of pharmacy, state health department).

14.2 Complaint Handling

Radiopharmaceutical facilities must develop and implement SOPs for handling complaints. Complaints may include concerns or reports on the quality and container labeling of, or possible adverse reactions to, a specific radiopharmaceutical.

A designated person must review all complaints to determine if they indicate potential quality problems with the radiopharmaceutical. If a complaint does, an investigation into the potential cause of the problem must be completed. The investigation must consider whether the quality problem could extend to other radiopharmaceuticals. Corrective action, if necessary, must be implemented for all potentially affected radiopharmaceuticals. Consider whether to initiate a recall of potentially affected radiopharmaceuticals and whether to cease sterile compounding until all underlying problems have been identified and corrected.

A readily retrievable record (written or electronic) of each complaint must be kept by the facility, regardless of the source of the complaint (e.g., e-mail, telephone, mail). The record must contain the name of the complainant, the date the complaint was received, the nature of the complaint, the response to the complaint, and, if known, the name and strength of the radiopharmaceutical and the assigned internal identification number (e.g., prescription, order, or lot number).

The record must also include the findings of any investigation and any follow-up. Records of complaints must be easily retrievable for review and evaluation for possible trends and must be retained in accordance with the record keeping requirements in *9. Documentation*. A radiopharmaceutical that is returned in connection with a complaint must be quarantined until it is destroyed after completion of the investigation and in accordance with applicable jurisdictional laws and regulations.

14.3 Adverse Event Reporting

Adverse events potentially associated with the quality of radiopharmaceuticals must be reported in accordance with the facility's SOPs and all applicable jurisdictional laws and regulations. In addition, adverse events potentially associated with the quality of the radiopharmaceutical preparation should be reported to the applicable jurisdictional regulatory body (e.g., state boards of pharmacy, state health departments, FDA's MedWatch program for human drugs).

GLOSSARY

Administration: The direct and immediate application of a radiopharmaceutical to a patient by injecting, infusing, ingesting, or otherwise providing a radiopharmaceutical in its final form.

Airlock: A space with interlocked doors, constructed to maintain air pressure control when items move between two adjoining areas.

Ante-room: An ISO Class 8 or cleaner area with fixed walls and doors where personnel hand hygiene, garbing procedures, and other activities that generate high particulate levels are performed. The ante-room is the transition area between the unclassified area in a facility and the classified buffer area.

Aseptic processing or preparation: A process by which separate, sterile components (e.g., drugs, containers, or closures) are brought together under conditions that maintain their sterility.

Aseptic technique: Methods utilized during the processing of radiopharmaceuticals to keep objects and areas free of microorganisms and thereby minimize infection risk to the patient. It is accomplished through practices that maintain the microbe count at a nearly irreducible number.

As low as (is) reasonably achievable (ALARA): The effort to maintain exposures to ionizing radiation as far below the dose limits as practical. These efforts should be consistent with the purpose for which the licensed activity is undertaken, in relation to utilization of licensed materials in the public interest. Limiting exposure time, using adequate shielding, and maintaining the most distance possible from all radioactive sources (i.e., time, distance, shielding) are the basic principles for successfully following ALARA guidelines.

Authorized nuclear pharmacist (ANP): A pharmacist recognized by the U.S. Nuclear Regulatory Commission or an Agreement State agency as having met training and experience requirements for the practice of nuclear pharmacy.

Authorized user (AU): A physician recognized by the U.S. Nuclear Regulatory Commission or an Agreement State agency as meeting training and experience requirements for specified medical uses of radioactive material.

Beyond-use date (BUD): The assigned date and time beyond which the radiopharmaceutical must not be administered.

Biological safety cabinet (BSC) Class II: A ventilated cabinet with an open front and inward and downward unidirectional HEPA-filtered airflow and HEPA-filtered exhaust.

Blood components: Any constituent of blood that is separated by physical or mechanical means (e.g., red cells, white cells, platelets)

Buffer area: An ISO Class 8 or cleaner area with fixed walls and doors where PEC(s) that generate and maintain an ISO Class 5 environment are physically located. The buffer area may only be accessed through the ante-room.

Chemical purity: The fraction of the total chemical species present in the radiopharmaceutical as the specified chemical component(s). A chemical impurity is the presence of an unwanted non-radioactive chemical.

Classified area: An area that maintains an air quality classification based on the ISO guidelines (i.e., ante-room, buffer area). See *ISO class*.

Cleaning agent: A material for the removal of residues (e.g., dirt, debris, microbes, and residual drugs or chemicals) from surfaces.

Compounding: The combining, mixing, pooling, or otherwise altering (excluding preparation with minor deviations) of a conventionally manufactured radiopharmaceutical or synthesizing/formulating a radiopharmaceutical from bulk drug substances and radionuclides. See *Preparation with minor deviations*.

Container–closure system: The packaging components that contain or come in contact with the radiopharmaceutical and maintain the integrity of the radiopharmaceutical contained within. Examples include (but are not limited to) vials, tubes and syringes.

Critical site: A location that includes any component or fluid pathway surface (e.g., vial septa, injection ports) or openings (e.g., needle hubs) that, when exposed is at risk for contamination by direct contact with air (e.g., ambient area or HEPA-filtered), moisture (e.g., oral and mucosal secretions), or touch.

Designated person: One or more individuals assigned to be responsible and accountable for the performance and operation of the radiopharmaceutical processing facility and for personnel who prepare, compound, dispense, and repackage radiopharmaceuticals.

Direct infusion system: An FDA-cleared medical device used to dispense and/or administer radiopharmaceuticals to multiple patients. The standards of this chapter pertain to devices with ambient air that lack and ISO Class 5 environment.

Direct processing area (DPA): An area within the ISO Class 5 PEC where critical sites are exposed to unidirectional HEPA-filtered air, also known as first air.

Disinfectant: A chemical or physical agent used on inanimate surfaces and objects to destroy microbiological contamination (e.g., fungi, viruses, and bacteria) when used in the appropriate concentrations and for the appropriate contact times. Sporicidal disinfectant agents are considered a special class of disinfectants that also are effective against bacterial endospores and fungal spores.

Dispensing: The manipulation or labeling of a radiopharmaceutical to render it in its final form for administration, typically obtained from a single-dose or multiple-dose container (e.g., withdrawing a volume of finished product or preparation from a vial into a syringe). Dispensing is performed under the supervision of a physician or pharmacist and for radiopharmaceuticals includes dilution with an appropriate diluent or adjusting the activity in an individual dosage.

Dose pooling: The combining of doses from two or more syringes to meet one patient's need, also see "repackaging".

Dose splitting: The splitting of a patient-ready unit dose for use with more than one patient.

Dynamic operating conditions: Conditions in the SRPA or classified area in which operating personnel are present and performing actual or simulated activities. The PEC should contain equipment and materials regularly used for radiopharmaceutical processing (e.g., low-lint absorbent pads, dose calibrator, syringe shields).

Expiration date: For conventionally manufactured radiopharmaceuticals, the specified date (and time) beyond which the product must not be administered. The expiration date is determined by the manufacturer.

First air: The air exiting the HEPA filter in a unidirectional air stream.

Garb: Gloves, gowns, shoe covers, head (covers ears and all hair) and facial hair covers, masks, and other items designed to reduce particle shedding from personnel and minimize the risk of microbiological contamination to radiopharmaceuticals.

High efficiency particulate air (HEPA) filtration: Using a tested and certified air filter designed to remove 99.97% of airborne particles measuring 0.3-micron or greater in diameter from the air passing through it.

Hot-cell: A device used for the shielding and containment of radioactive materials. The shielding material(s) (e.g., lead) is generally incorporated into the structure of the unit itself. Radiopharmaceutical personnel carry out the majority of the tasks within the hot-cell from the exterior of the unit. This is accomplished by the use of remote manipulation systems (e.g., manipulator arms, automated dispensing system) of various designs. Numerous air quality configurations of the hot-cell may exist, including integrated HEPA filtration systems to render all or a specified portion (DPA) of the device capable of certifying to a controlled ISO Class 5 environment. In other situations, the hot-cell offers only radiation protection and a laminar flow PEC, capable of achieving an ISO Class 5 environment, is placed within the enclosure to allow for safe aseptic manipulations. A hot-cell may also be referred to by other designations (e.g., shielded isolator with laminar flow, PET dispensing station, manipulator hot-cell, shielded isolators for dispensing, radiopharmaceutical dispensing isolator).

Hot lab: Unclassified radiopharmaceutical processing area located within a hospital or clinical site that is only appropriate for immediate use radiopharmaceuticals if there is not an ISO 5 PEC within SRPA located within the area.

Immediate use: A preparation (including preparations with minor deviations) and/or dispensing of a sterile radiopharmaceutical that is limited for a single patient. Only sterile conventionally manufactured drug products (e.g., NDA, ANDA) or drugs produced under an approved IND or RDRC protocol may be used. Administration must begin within 1 hour of the first container puncture or exposure of any critical site involved (e.g., syringe tip, needle hub or needle) to ambient air, whichever is first.

Individual dose (unit dose): A radiopharmaceutical in its final form ready for administration (e.g., capsule, sterile solution in a syringe) consisting of the amount (dose) prescribed, ordered, or other intended for an individual patient or research subject.

Inverse square law: The specified physical quantity or intensity of a radiation emission is inversely proportional to the square of the distance from the source of the emission.

ISO class: A quality classification from the International Organization for Standardization based on quantity and size of particles per volume of air.

Kit: Conventionally manufactured package containing all ingredients required to prepare a radiopharmaceutical with the exception of the radionuclide.

Kit-splitting (fractionation): The act of dividing the contents of a kit vial and transferring aliquots into other containers for storage and subsequent radiolabeling.

Ligand: An ion or molecule that incorporates a metal atom to form a coordination complex.

Line of demarcation: A visible line on the floor that separates the clean and less clean sides of the ante-room.

Low-lint wiper: A wiper exhibiting few, if any, fibers or other particulates, visible without magnification, which are separate from, or easily removed from, the wiper material in a dry condition.

Master Formulation Record (MFR): A document or set of documents specifying the starting materials with their quantities and the packaging materials, together with a description of the procedures and precautions required to produce a specified quantity of a finished preparations as well as the processing instructions, including the in-process controls.

Media-fill test: A simulation used to qualify processes and personnel engaged in sterile radiopharmaceutical processing to ensure that the processes and personnel are able to prepare radiopharmaceuticals without microbiological contamination.

Molar mass: The measured mass that is attained from a molar amount of a given substance (e.g., element, compound). It is generally expressed with units such as g/mol and kg/mol.

Multiple-dose container: A container of a radiopharmaceutical for administration that is designed to contain more than one patient dose of the radiopharmaceutical.

Negative-pressure area: An area that is maintained at lower pressure than the adjacent spaces, and therefore the net airflow is into the area. This area is appropriate for volatile or gaseous radionuclides and radiopharmaceuticals (e.g., I-131 NaI, N-13 ammonia) and intended to lend a measure of protection for the radiation workers and the general public.

One-step disinfectant cleaner: A product with an EPA-registered claim (or equivalent) that it can clean and disinfect a nonporous surface in the presence of light to moderate organic soiling without a separate cleaning step.

Pass-through: An enclosure with sealed doors on both sides to ensure that both doors are not opened at the same time. The pass-through is positioned between two spaces creating an airlock for the purpose of minimizing particulate transfer while moving materials from one space to another.

Perimeter: A visible demarcation on the floor that defines the boundaries of the SRPA.

Positive-pressure area: An area that is maintained at higher pressure than the adjacent spaces, and therefore the net airflow is out of the area.

Preparation: The act of combining a conventionally manufactured kit with a conventionally manufactured radionuclide following manufacturer's recommended instructions. Mixing, reconstituting, combining, diluting, or repackaging of a radiopharmaceutical, or other such acts, performed in accordance with directions contained in the FDA-approved labeling.

Preparation with minor deviations: The act of preparing a conventionally manufactured kit with a conventionally manufactured radionuclide with volume, and/or radioactivity, and/or step-by-step deviations from the manufacturers recommended labeling while ensuring that the final preparation maintains appropriate radiochemical and radionuclidic purity for the entirety of the BUD. Examples of minor deviations include, but are not limited to, altering the amount of activity or volume added to the vial, changes in step-by-step operations (e.g., dilute Tc-99m solution after, rather than before, addition to the vial, use of a venting needle or filter), using alternative devices or equipment (e.g., a heating block rather than a hot water bath), and using alternative radiochemical purity testing methods.

Primary engineering control (PEC): A device or zone that provides an ISO Class 5 air quality environment for sterile processing.

Pyrogen: A substance that induces a febrile reaction in a patient.

Quality assurance (QA): The system of procedures, activities, and oversight that ensures that radiopharmaceutical processing consistently meets quality standards.

Quality control (QC): The sampling, testing, and documentation of results that, taken together, ensure that specifications have been met before release of the radiopharmaceutical.

Radioactive materials (RAM) license: A document(s) issued by the US NRC or an Agreement State agency that authorizes various activities involving the use of radioactive materials. These uses can include possession, research and development, distribution, medical use, and other purposes not included in this list. Only those activities specifically authorized are allowed.

Radioassay: Measurement of the quantity of radioactivity present in a container using a suitable and calibrated instrument, such as a well-type ionization chamber (i.e., dose calibrator).

Radiochemical purity: The ratio, expressed as a percentage, of the radioactivity of the intended active radiopharmaceutical ingredient to the total radioactivity of all radioactive ingredients and impurities present in the radiopharmaceutical preparation (see *Radioactivity* ⟨821⟩).

Radionuclidic purity: The ratio, expressed as a percentage, of the radioactivity of the intended radionuclide to the total radioactivity of all radionuclides in the radiopharmaceutical preparation (see ⟨821⟩).

Radiopharmaceutical (radiopharmaceutical preparation/radioactive drug): (See ⟨821⟩.) A finished dosage form that contains a radioactive substance in association with one or more other ingredients and that is intended to diagnose, stage a disease, monitor treatment, or provide therapy. A radiopharmaceutical includes any non-radioactive reagent kit or radionuclide generator that is intended to be used in the preparation of any such substance. The terms "radiopharmaceutical" and "radioactive drug" are commonly used interchangeably.

Repackaging: The act of removing a conventionally manufactured radiopharmaceutical from the container in which it was distributed by the original manufacturer and placing it into a different container without further manipulation of the product. Repackaging also includes the act of placing the contents of multiple containers (e.g., vials) of the same finished drug product into one container, as long as the container does not include other ingredients. Radiopharmaceutical manipulation in any other way, including reconstitution, dilution, mixing, or combination with another ingredient, is not considered repackaging.

Restricted area: Any area to which access is controlled for the protection of individuals from exposures to radiation and radioactive materials.

Secondary engineering control (SEC): The area where the PEC is placed (e.g., a classified area or an SRPA). It incorporates specific design and operational parameters required to minimize the risk of microbial contamination.

Segregated radiopharmaceutical processing area (SRPA): A designated, unclassified space, area, or room with a defined (by facility procedures) perimeter that contains a PEC. An SRPA is only suitable for radiopharmaceutical preparation (with and without minor deviations), dispensing, and repackaging. If the SRPA is used to elute radionuclide generators it must have ISO Class 8 particle count non-viable particle count air quality.

Shielding: Barriers of appropriate radiation attenuating material, used for radiopharmaceuticals, to protect the personnel. These barriers can be general in nature (e.g., L-block, hot-cell), as to afford protection from a radiation field, or specific to a container used to hold a particular radiopharmaceutical (e.g., syringe shield, vial shields, "pigs").

Single-dose container: A container of a radiopharmaceutical for administration that is designed for use with a single patient as a single administration.

Specific activity: The radioactivity of a radionuclide per unit mass of the compound involved with the radionuclide (see *Radioactivity—Theory and Practice* ⟨1821⟩). The units of specific activity involve those for the activity (e.g., mCi, MBq, Ci, GBq) and those for the unit of mass (e.g., µg, mmol); expressed on an activity per mass basis (e.g., mCi/µg, MBq/µg, Ci/mmol, GBq/mmol).

Sporicidal agent: A chemical or physical agent that destroys bacterial and fungal spores when used in sufficient concentration for a specified contact time. It is expected to kill all vegetative microorganisms.

Start of preparation: Time at which a vial septum is punctured or a component container is opened (e.g., removal of cap on a pre-filled syringe), whichever comes first.

Sterility: The absence of viable microorganisms.

Strength: The radioactivity concentration of the radiopharmaceutical at the calibration time (see ⟨821⟩). Strength is expressed as the quantity of radioactivity on a volume basis (e.g., mCi/mL or MBq/mL).

Unclassified space: A space not required to meet any ISO air cleanliness classification.

Unrestricted area: An area in which a person should not be exposed to radiation levels in excess of 2 millirems in any 1 h from external sources.

Use-by time: For radiopharmaceuticals prepared from kits, the time period after preparation during which the radiopharmaceutical should be used or administered, as suggested or stated in the manufacturer's prescribing information.

APPENDIX

Abbreviations

ACPH	Air changes per hour
ALARA	As low as reasonably achievable
ANDA	Abbreviated new drug application
ANP	Authorized nuclear pharmacist
AU	Authorized user
BLA	Biologics license application
BSC	Biological safety cabinet
BUD	Beyond-use date
CETA	Controlled Environment Testing Association
cfu	Colony-forming unit
CoA	Certificate of analysis
DPA	Direct processing area
EPA	Environmental Protection Agency
FDA	Food and Drug Administration
FDCA	Food, Drug, and Cosmetic Act
HEPA	High-efficiency particulate air
HVAC	Heating, ventilation, and air conditioning
IND	Investigational new drug
IPA	Isopropyl alcohol
ISO	International Organization for Standardization
LAFW	Laminar airflow workbench
MAA	Macroaggregated albumin
MEA	Malt extract agar
MFR	Master Formulation Record
NDA	New drug application

Abbreviations *(continued)*

NRC	Nuclear Regulatory Commission
PEC	Primary engineering control
PET	Positron emission tomography
RAM	Radioactive material
RDRC	Radioactive drug research committee
RH	Relative humidity
SDA	Sabouraud dextrose agar
SEC	Secondary engineering control
SOP	Standard operating procedure
SRPA	Segregated radiopharmaceutical processing area
TSA	Trypticase soy agar