Medication Safety Committee Meeting

October 17, 2019

California Society of Hospital Pharmacists Seminar

Disneyland Hotel, Western Room, Frontier Tower

Anaheim, CA

Conference Call Option:

800-882-3610 Passcode: 4206832#

Meeting Book - Medication Safety Committee Meeting

Medication Safety Committee Meeting Agenda

12:00 I. CALL TO ORDER/INTRODUCTIONS
Hanni

12:05 II. OLD BUSINESS

1:15 III. NEW BUSINESS

1:30 IV. LEGISLATION

A. Pharmacy Bills
Bartleson

1:45 V. STANDING REPORTS

A. Board of Pharmacy
Sodergren

B. California Society of Heath-System Pharmacists (CSHP)
Stephens

C. California Department of Public Health (CDPH)
Christensen/Lee/Woo

D. California Association of Health Facilities
Owens

VI. INFORMATION ONLY

VII. NEXT MEETING

2:00 VIII. ADJOURNMENT
Hanni

CALIFORNIA HOSPITAL ASSOCIATION

Providing Leadership in Health Policy and Advocacy

DATE: October 17, 2019

TO: Medication Safety Committee Members

FROM: BJ Bartleson, MS, RN, NEA-BC, Vice President, Nursing & Clinical Services

SUBJECT: Sterile Compounding Updates and Next Steps

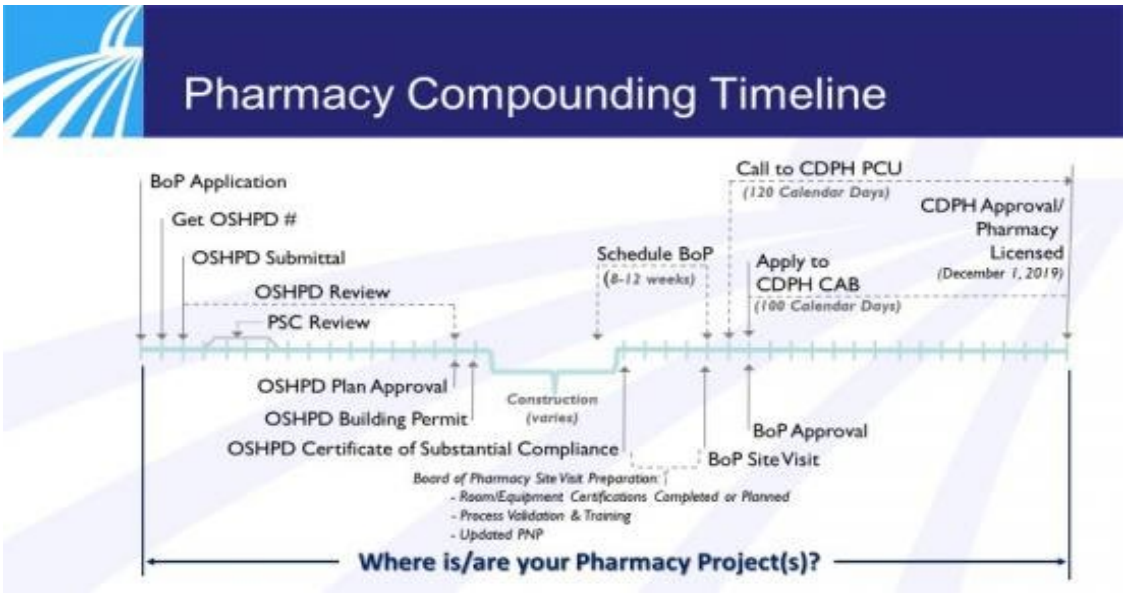
SUMMARY

At our July 17th meeting we discussed the need to identify gaps, barriers and issues preventing hospitals' successful compliance to USP upcoming sterile compounding requirements. A hospital CEO memo was distributed, (Attachment #1) and hospital PIC's asked to respond to a survey of key areas of the sterile compounding clean room construction upgrade and process. The survey summary and results are attached, (Attachment #2)

On September 23, 2019, USP announced the postponement of the official dates of the revised 795 and 795 and the new general chapter 825 until further notice (Attachments #3, 4, 5, 6). In the interim, the current official chapters of 797 (last revised in 2014) and 797 (last revised in 2008) including the section Radiopharmaceuticals as CSPs will remain official. The decisions on the appeals to 795, 797 and 825 do not foreclose the possibility of future revisions to these chapters.

General Chapter 800 is not subject to any pending appeals and will become official on December 1, 2019. During the postponement and pending resolution of the appeals of 795 and 797, 800 is informational and not compendially applicable. USP encourages utilization of 800 in the interest of advancing public health.

Despite the USP deadline postponement, and numerous hospitals undergoing construction, CHA will be hosting a Sterile Compounding Webinar on November 12, 2019, from 1-3 pm to assist hospitals in continuing their pharmacy sterile compounding construction activities as planned, in order to meet USP standards once they become official. The webinar will include officials from the California Department of Public Health (CDPH), Board of Pharmacy (BoP), and Office of Statewide Health Planning and Development (OSHPD), who will offer their insights on avoiding lengthy and costly delays.



The Board of Pharmacy continues to provide pre-regulatory comment sessions and revisions to Article 7 Sterile Compounding in Pharmacies- See attachment #7)

DISCUSSION

1. Are there outstanding issues that members need help with regarding sterile compounding requirements?
2. Do you have additional revisions you want to offer to the BoP draft regulations attached?

ACTION REQESTED

- Finalize suggested revisions for BoP Sterile Compounding regulations.

Attachments: CHA CEO Memo
CHA Sterile Compounding Survey Summary
USP Notification
Revised USP 795
Revised USP 797
Revised USP 825
BoP Regulations Draft

BJB:br

Barbara Roth

From: Carmela Coyle <info@calhospital.org>
Sent: Thursday, August 1, 2019 8:31 AM
To: Barbara Roth
Subject: Action Needed: Complete Survey on New or Remodeled Pharmacy Clean Room Projects

We need your help. We know many of you need more time to meet new federal standards for new or remodeled pharmacy clean room projects. **Help us educate lawmakers and regulators on compliance challenges by having your pharmacist-in-charge complete this survey by August 14.**

Where we stand now: if these construction projects are not finalized by December 1, 2019, you could be at risk for survey citation and may lose your ability to perform sterile compounding. CHA, together with the American Hospital Association, is telling accreditors and the Centers for Medicare & Medicaid Services of the challenges these new standards and their implementation deadline present. Information gathered in this survey will inform our efforts to seek a delay in enforcement.

For more details about the standards and requirements, as well as how you can help, visit the CHA website. We know this is a complex issue, and we're on it for you. Thanks for your help!

Carmela

This message was sent to CHA member hospital CEOs, chief operating officers, chief nursing officers, and pharmacy staff.

CHA Medication Safety Sterile Compounding Survey Report

Executive Summary

CHA surveyed approximately 148 hospitals with 208 clean rooms. Hospitals answered for each of their clean rooms undergoing or planning to undergo construction changes to meet USP Sterile Compounding requirements. The survey questions were focused on key components of the construction process and regulatory requirements to meet the December 2019 deadline.

The questionnaire was composed of 9 questions on barriers hospitals face in the three phases of the construction process: Barriers to starting construction, barriers to completing the construction and barriers to full construction completion and regulatory signoff.

Barriers to Initiation of Construction Process

While financial constraints were a major reason for construction delays, many hospitals are undecided and attempting to use alternative sterile compounding methods.

One hundred and one (101) clean rooms identified "other issues" as barriers, the "other" items included construction delays, project underway, physical space issues, construction completion, regulatory issues, undecided and not applicable. Twenty-five (25) potential clean room conversions are using alternative methods to compound for example, moving to immediate use only, using a CAI, finding an alternative location and outsourcing. Twenty-one (21) clean rooms are undecided because they are going through new ownership, are delayed in their internal capital projects and or weighing options.

Outsourcing and Vendor

Over 60 clean rooms are engaged in outsourcing activity and the highest number use CAPS as their outsourcing vendor.

Mobile Compounding Unit

Sixteen or 8% of respondents are using a mobile compounding unit.

Barriers to Construction Completion

Forty-nine (49) clean rooms are under construction while several are working through governance approval, financing, design and OSHPD sign off. Of those who answered "other", 22% (12) are awaiting regulatory agency approval. Almost 34% (41) indicated that construction would be complete by December 1, 2019 and another 34% (41) anticipating construction completion by the end of 2020. Almost 85% who have completed construction have also received OSHPD approval. Over a third (34%) (39) of respondents anticipate having construction completed and all regulatory approvals by December 2019 deadline. Of those missing the deadline, 40% (46) expect to be complete by the end of 2020.

Most Significant Barriers to Timely Completion

Lack of funding was identified by more than 75% (128) of respondents as a significant barrier to timely completion. The inability to obtain skilled contractors and or architects was also listed by over 60% (104) as a barrier. A lack of pharmacy or staff leadership to fully inform the process change was seen as the least significant barrier to timely completion of the project (49%) (82). Over 82 respondents provided comments, of which 47 (57%) mentioned a problem with one of the regulatory agencies, Office of Statewide Planning and Development (OSHPD), Board of Pharmacy (BoP) or California Department of Public Health (CDPH) as a problem.

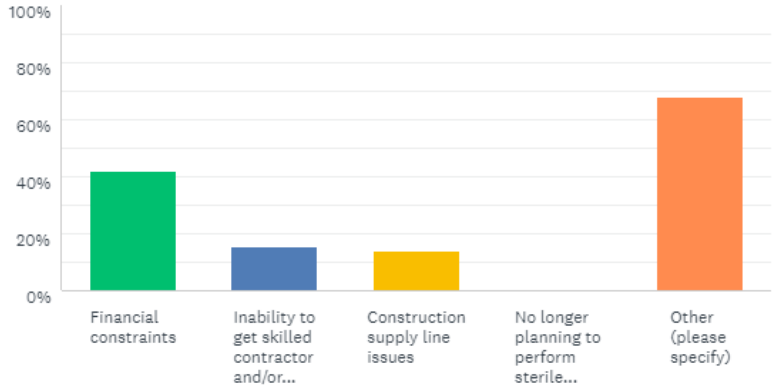
CHA Medication Safety Sterile Compounding Survey Results

Question #1 - How many pharmacy clean rooms are currently performing sterile compounding in this hospital? If more than one they will complete question for each clean room – data collected on 8/16/2019, from approximately 148 hospitals - total number of clean rooms = 208

Question #2 – if the construction process has not yet been started to meet the new standards, please identify the reasons why

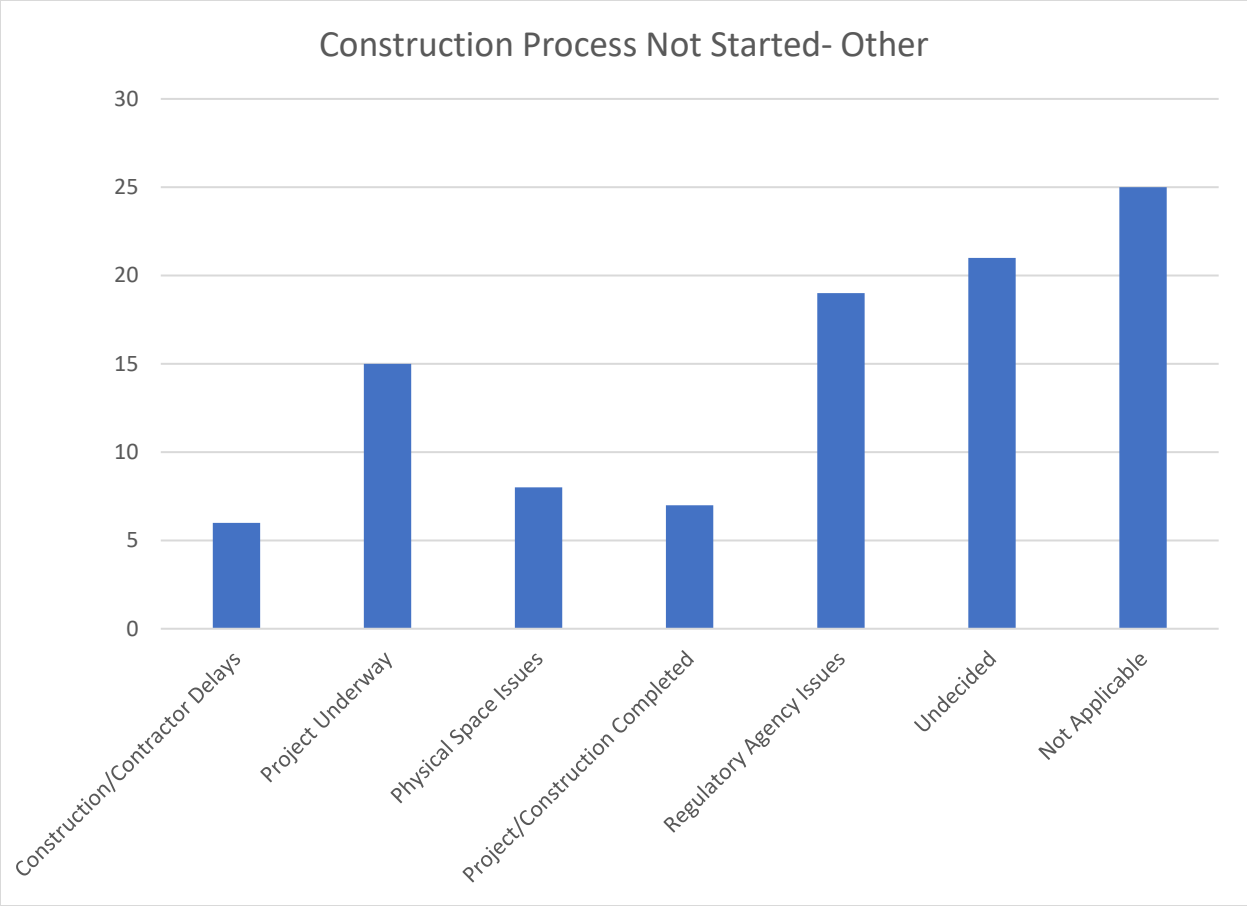
Clean Room 1. If the construction process has not yet been started to meet the new standards, please identify the reasons why. (Check all that apply)

Answered: 148 Skipped: 60

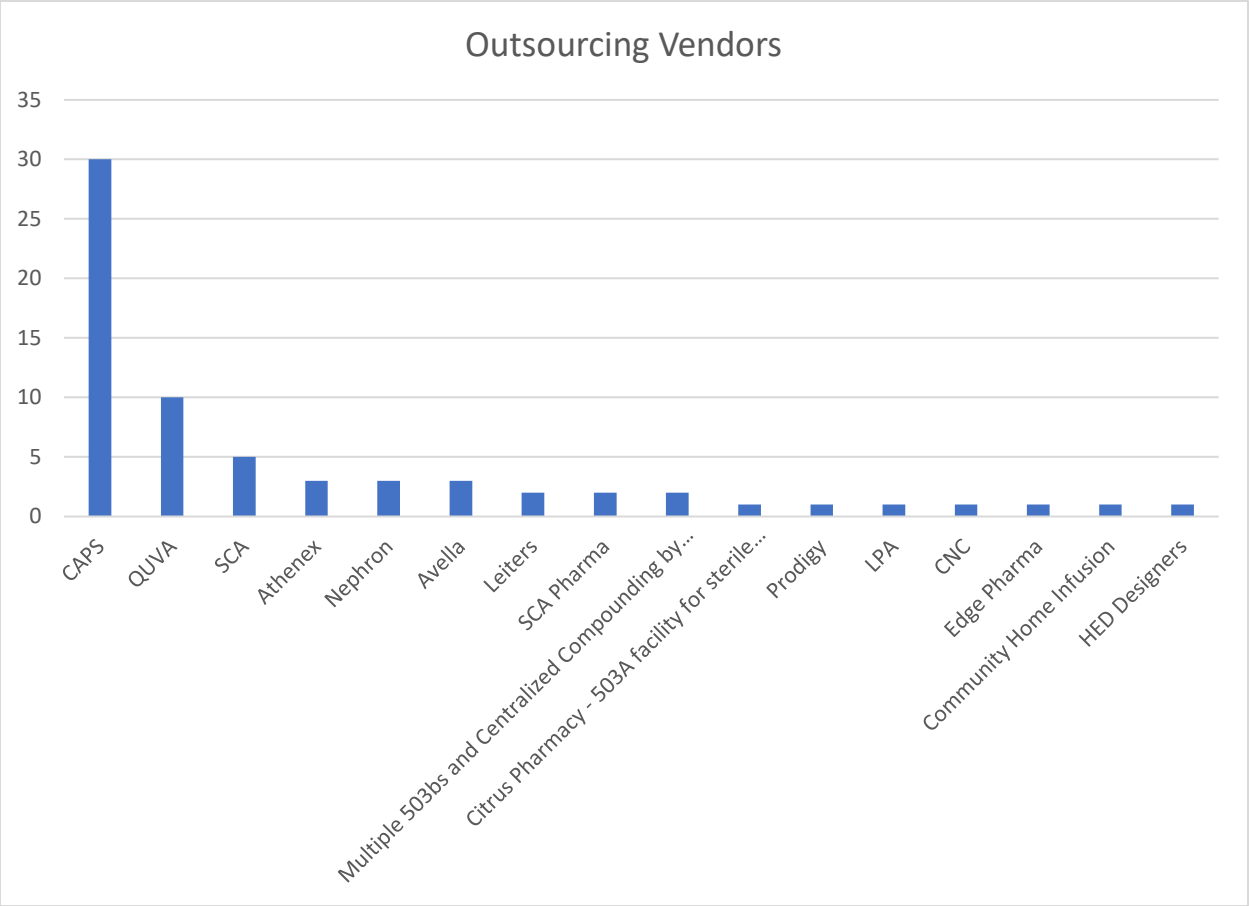


ANSWER CHOICES		RESPONSES	
Financial constraints		41.89%	62
Inability to get skilled contractor and/or architects		15.54%	23
Construction supply line issues		14.19%	21
No longer planning to perform sterile compounding on site		0.68%	1
Other (please specify)	Responses	68.24%	101
Total Respondents: 148			

- Financial constraints were identified as a major reason for construction delays.
- The inability to get skilled contractors and/or architects, along with construction supply line issues, each represented less than 20% (23 and 21) as reasons for delays in construction.
- For respondents listing “other” for delays, most have not yet decided whether or when to begin construction (see graph below).


Construction Process Not Started- Other
30
25
20
15
10
5
0
Construction/Contractor Delays
Project Underway
Physical Space Issues
Project/Construction Completed
Regulatory Agency Issues
Undecided
Not Applicable

Question #3 - If outsourcing, please identify outsourcing vendor



- Almost 45% (30) of respondents identified CAPS as their chosen vendor for outsourcing sterile compounded pharmaceuticals.

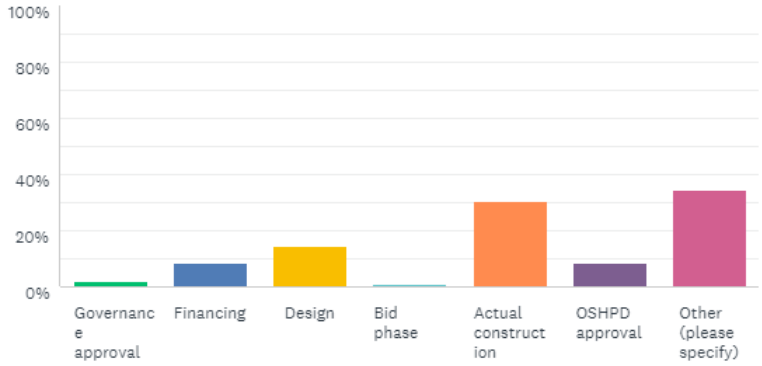
Question #4 - Is a mobile sterile compounding unit currently being used or in the plans for future use?

- 8% (16) are using a mobile sterile compounding unit.

Questions #5 – If construction is underway, please identify where you are in the current process.

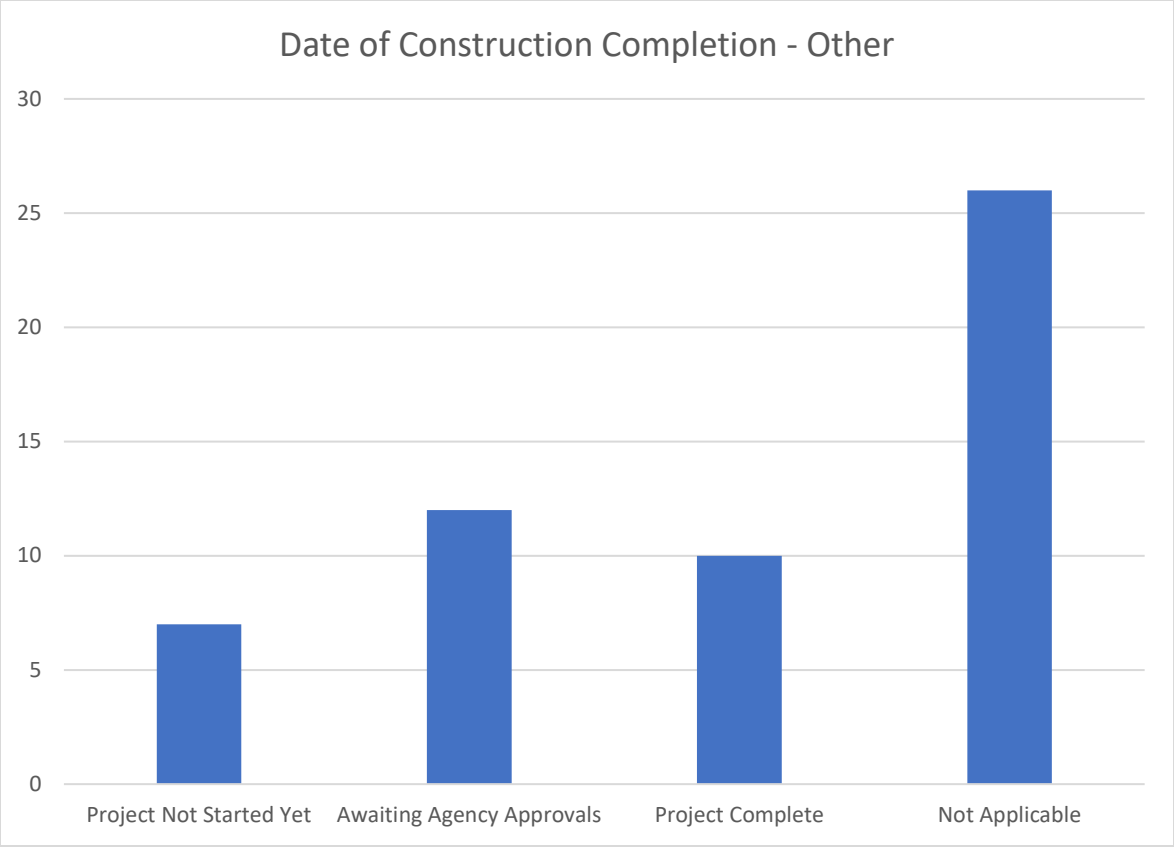
If construction is underway, please identify where you are in the current process.

Answered: 160 Skipped: 47

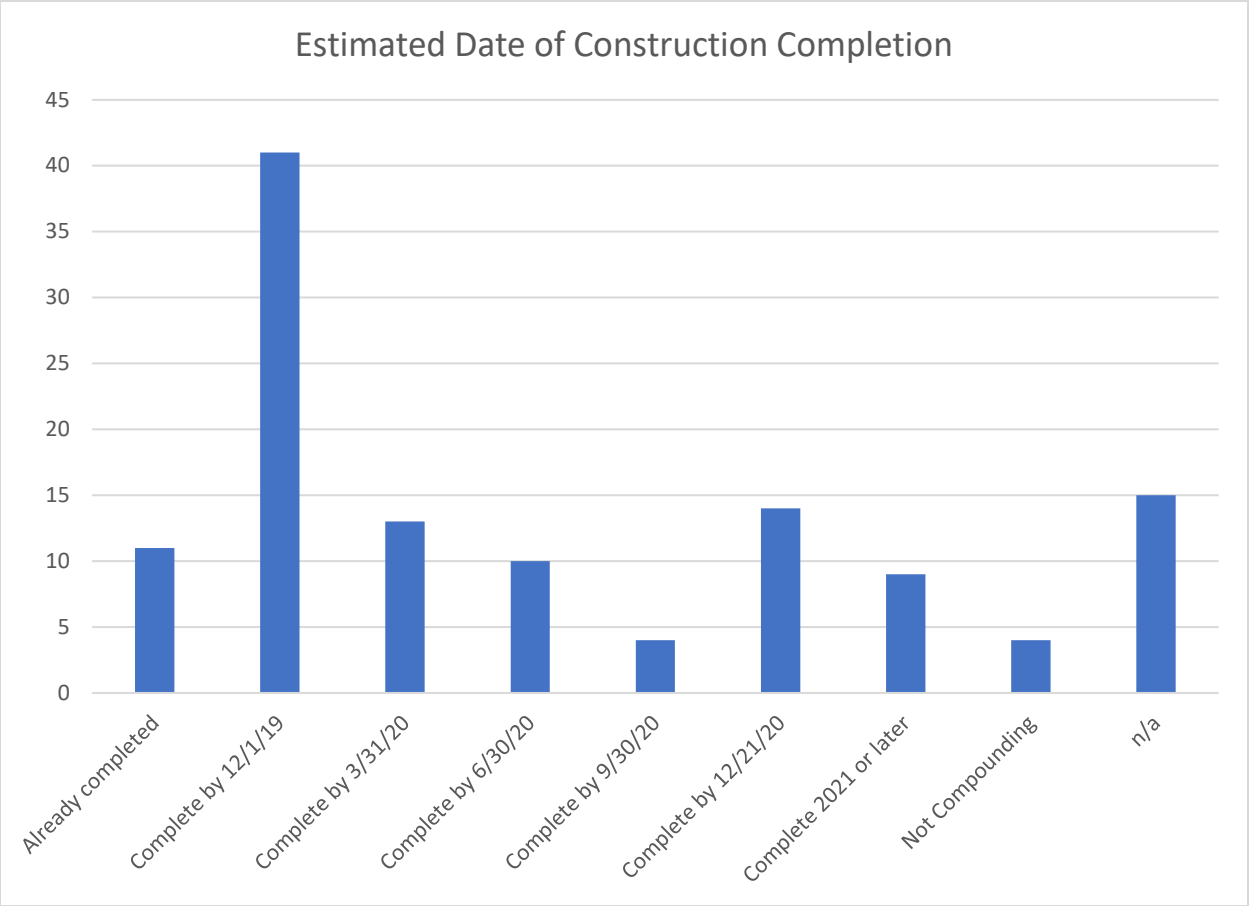


ANSWER CHOICES		RESPONSES	
Governance approval		1.88%	3
Financing		8.75%	14
Design		14.37%	23
Bid phase		1.25%	2
Actual construction		30.63%	49
OSHPD approval		8.75%	14
Other (please specify)	Responses	34.38%	55
TOTAL			160

- Most respondents have already begun the actual construction process.
- Of those who answered “other”, 22% (12) are awaiting agency approval (see graph below).


Date of Construction Completion - Other
30
25
20
15
10
5
0
Project Not Started Yet
Awaiting Agency Approvals
Project Complete
Not Applicable

Question #6 – What is the estimated date of construction completion?

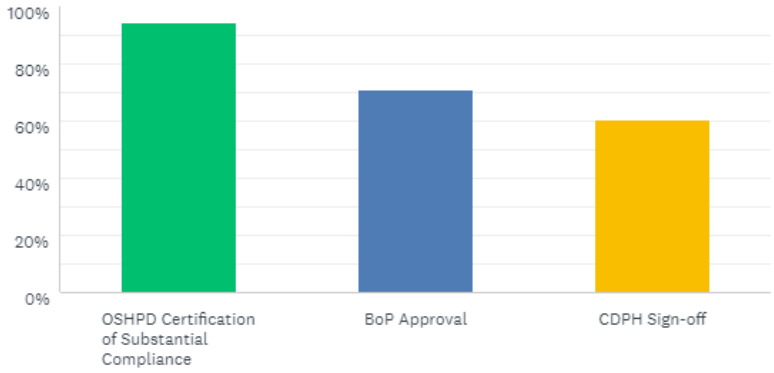


- Almost 34% (41) indicated that construction would be complete by the December 1, 2019 deadline.
- Another 34% (41) anticipate construction completion by the end of 2020.

Question #7 - If construction is complete, have the following approvals been obtained?

If construction is complete, have the following approvals been obtained? (Check all that apply).

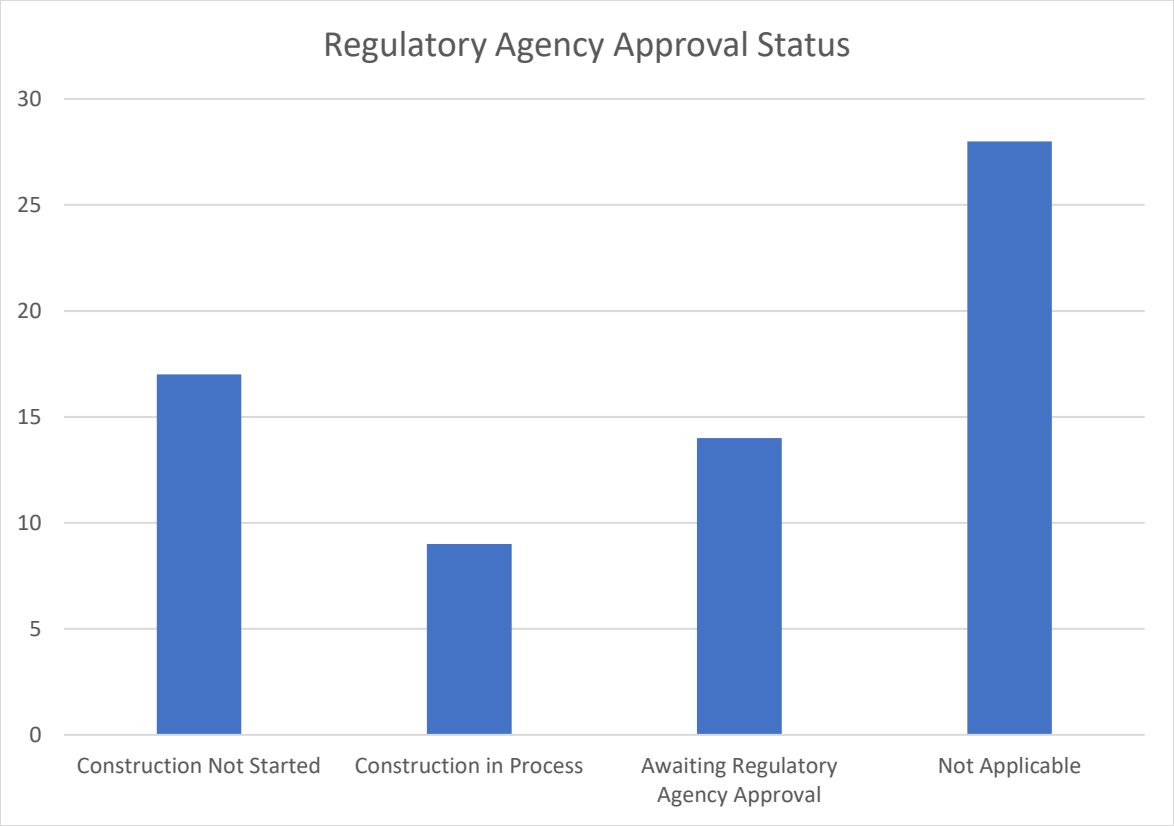
Answered: 38 Skipped: 170



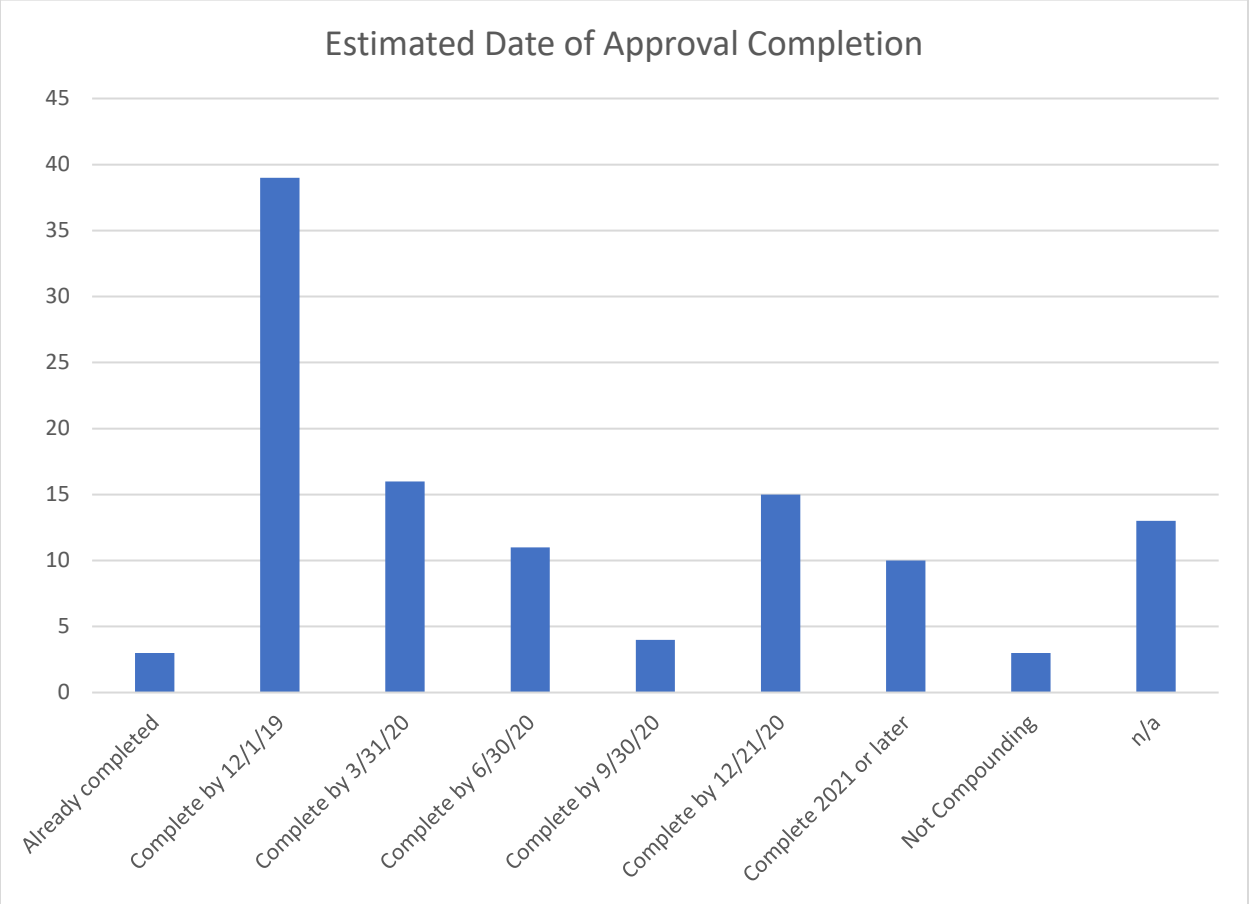
ANSWER CHOICES	RESPONSES	
OSHPD Certification of Substantial Compliance	94.74%	36
BoP Approval	71.05%	27
CDPH Sign-off	60.53%	23
Total Respondents: 38		

Comments (68)

- Almost 95% (36) who have completed construction have also received OSHPD approval.


Regulatory Agency Approval Status
30
25
20
15
10
5
0
Construction Not Started
Construction in Process
Awaiting Regulatory Agency Approval
Not Applicable

Question #8 – What is your estimated target date for all the following to be completed: OSHPD, BoP, and CDPH approvals?

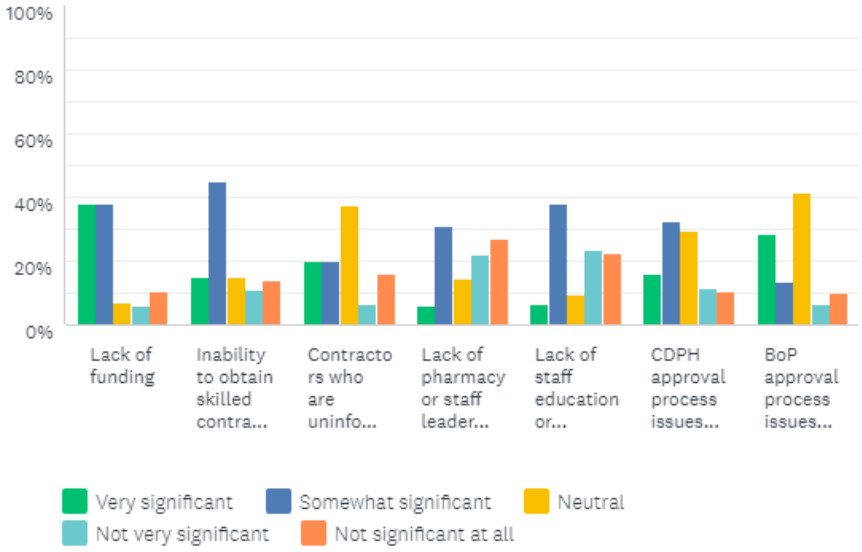


- Over a third (39) of respondents anticipate having construction completed and all regulatory approvals by the December 1, 2019 deadline.
- Of those missing the deadline, 40% (46) expect to be complete by the end of 2020.

Question #9 – Please identify the most significant barriers to timely completion

Please identify the most significant barriers to timely completion. (Check all that apply and rank)

Answered: 181 Skipped: 27



- Lack of funding was identified by more than 75% (128) of respondents as a significant barrier to timely completion.
- The inability to obtain skilled contractors and/or architects was also listed by over 60% (104) as a barrier.
- A lack of pharmacy or staff leadership to fully inform the process change was seen as the least significant barrier to timely completion of the project (49%) (82).

	VERY SIGNIFICANT	SOMEWHAT SIGNIFICANT	NEUTRAL	NOT VERY SIGNIFICANT	NOT SIGNIFICANT AT ALL	TOTAL
Lack of funding	38.10% 64	38.10% 64	7.14% 12	5.95% 10	10.71% 18	168
Inability to obtain skilled contractors and/or architects	15.03% 26	45.09% 78	15.03% 26	10.98% 19	13.87% 24	173
Contractors who are uninformed of the USP standards	20.12% 34	20.12% 34	37.28% 63	6.51% 11	15.98% 27	169
Lack of pharmacy or staff leadership to fully inform the process change	5.95% 10	30.95% 52	14.29% 24	22.02% 37	26.79% 45	168
Lack of staff education or understanding regarding USP requirements to adequately oversee the project	6.47% 11	38.24% 65	9.41% 16	23.53% 40	22.35% 38	170
CDPH approval process issues, if so please explain in comment section	16.18% 28	32.37% 56	29.48% 51	11.56% 20	10.40% 18	173
BoP approval process issues, if so please explain in comment section	28.65% 49	13.45% 23	41.52% 71	6.43% 11	9.94% 17	171

American Hospital Association™
Advancing Health in America

Special Bulletin

September 23, 2019

United States Pharmacopeia Delays Official Effective Dates of New and Revised Compounding Standards

The United States Pharmacopeia (USP) today notified stakeholders that it is postponing the official effective dates of several new and revised standards pertaining to pharmaceutical handling until further notice while it reviews appeals to the standards. Those standards include general chapters <795> (Pharmaceutical Compounding – Nonsterile Preparations), <797> (Pharmaceutical Compounding – Sterile Preparations), and <825> (Radiopharmaceuticals – Preparation, Compounding, Dispensing, and Repackaging). In addition, due to the pending appeals, USP new general chapter <800> (Hazardous Drugs Handling in Healthcare Settings) will remain official, but only informational and will not be applicable until the appeals process is complete.

Key Takeaways

This update from USP means:

- Appeals are pending on published revisions to USP <795> and <797>, as well as to new general chapter <825>.
- During the appeals process, the official effective dates (previously Dec. 1, 2019) for USP <795>, <797> and <825> will be postponed until further notice.
- USP <800> is not subject to an appeal, but will not be applicable while the appeals process for the other chapters is ongoing. USP <800> only will be informational for the time being.

AHA Take: The AHA in November 2018 urged USP to delay the official effective dates of both USP <797> and <800> due to expedited implementation and compliance concerns. Today's update provides necessary relief for hospitals and health systems. While USP is not an enforcement agency, we continue to develop and share tools and resources for implementation and compliance, including a Regulatory Advisory we put out last week before today's announcement. In addition, we remain committed to advocating with the Centers for Medicare & Medicaid Services (CMS) and accrediting organizations to provide more clarity about expectations for compliance and the timing of when full compliance is expected given that many actions required for full compliance would require substantial time and resources. Nonetheless, protecting health care personnel from harm resulting from occupational exposure to environmental hazards is a top priority for hospitals and health systems.

HIGHLIGHTS OF THE UPDATE

Formal appeals were submitted to the USP with regard to revisions to general chapters <795> and <797>, as well as new general chapter <825>. In accordance with USP bylaws, the official

dates for the revisions and new general chapter will be postponed until further notice. It is important to note that the decisions on the appeals do not foreclose future revisions to these chapters. In addition, while new general chapter <800> is not subject to any pending appeals, the associated Dec. 1, 2019 official date will not be compendially applicable, meaning that <800> will serve only as information for the time being. During the postponement and pending resolution of the appeals of <795> and <797>, the current official chapters will remain official. <797> was last revised in 2014 and <797> was last revised in 2008.

FURTHER QUESTIONS

Prior to the notice of appeals, the AHA has and will continue to advocate with CMS and accrediting organizations for additional clarity on these new standards, specifically <797> and <800>. As we gather more information on this issue, we will keep members informed. Please stay tuned for more information concerning scheduled webinars on these standards. In addition, members are advised to reach out to their state boards of pharmacy concerning the applicability of <800> in their respective states. If you have further questions, please contact Mark Howell, senior associate director of policy, at mhowell@aha.org.

2019

USP General Chapter <795> *Pharmaceutical Compounding – Nonsterile Preparations*

Reprinted from USP 42—NF 37

Links for Supplemental Resources

- Information on USP General Chapter <795>
- USP General Chapter Compounding FAQs
- USP General Chapter <795> Education Courses
- Sign up for USP Updates

This text is a courtesy copy of General Chapter <795> Pharmaceutical Compounding – Nonsterile Preparations, intended to be used as an informational tool and resource only. Please refer to the current edition of the USP-NF for official text.

This chapter alone is not sufficient for a comprehensive approach to pharmaceutical compounding – nonsterile preparations. Additional chapters are required for complete implementation; see USP Compounding Compendium or USP-NF.

⟨795⟩ PHARMACEUTICAL COMPOUNDING—NONSTERILE PREPARATIONS

Change to read:

1. INTRODUCTION AND SCOPE

This chapter describes the minimum standards to be followed when preparing 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 or bulk drug substance to create a nonsterile medication.

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

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, ointments)
- Nasal and sinus preparations intended for local application (i.e., nasal sprays and nasal irrigation)
- Otic preparations

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:

Administration: Preparation of a single dose for a single patient when administration will begin within 4 hours of beginning the preparation is not required to meet the standards in this chapter.

Nonsterile radiopharmaceuticals: Compounding of nonsterile radiopharmaceuticals is not required to meet the standards in this chapter and 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 is not required to meet the standards in this chapter.

Repackaging: Repackaging of conventionally manufactured drug products is not required to meet the standards in this chapter (see *Good Repackaging Practices* ⟨1178⟩).

Splitting tablets: Breaking or cutting a tablet into smaller portions is not required to meet the standards in this chapter.

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, 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 of CNSPs must also comply with laws and regulations of the applicable regulatory jurisdiction.

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 of 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 an SOP. If the compounding facility has only one person responsible for all of the compounding in the facility, then that person is the designated person.

2. PERSONNEL TRAINING AND EVALUATION

All personnel involved in the preparation and handling of CNSPs must be initially trained, must demonstrate competency, and must undergo refresher training every 12 months. Training and competency of personnel must be documented as described in *15. Documentation*.

A designated person must oversee a training program that describes the required training, the frequency of training, and the process for evaluating the competency of personnel involved in nonsterile compounding and handling of CNSPs. This program must equip personnel with knowledge and training in the required skills necessary to perform their assigned tasks.

Before beginning to prepare CNSPs independently, all compounding personnel must complete training and be able to demonstrate proficiency in the principles and hands-on skills of nonsterile manipulations for the type of compounding they will be performing. Proficiency must be demonstrated 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., Master Formulation Records and Compounding Records)

Steps in the training procedure must include the following:

- Read and understand this chapter, other applicable standards, and other relevant literature
- Understand and interpret Safety Data Sheets (SDSs) and, if applicable, Certificates of Analysis (COA)
- Read and understand procedures related to their compounding duties

A designated person must oversee the training of personnel. 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, but under the direct supervision of the designated person(s) and/or 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 trainer must document that the personnel has been trained and successfully completed competency assessments (see *15. Documentation*).

In addition to the initial and annual competency training and evaluation described in this section, a designated person should monitor and observe compounding activities and must take immediate corrective action if deficient practices are observed. SOPs must describe procedures for the monitoring and observing of 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 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 or oozing sores, conjunctivitis, or active respiratory infection). Individuals 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 CNSP and the environment.

3.1 Personnel Preparation

Personnel engaged in compounding must maintain hand hygiene and maintain 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, 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, rings that may tear gloves)
- Remove earbuds or headphones

The designated person(s) may permit accommodations as long as the quality of the environment and CNSP will not be affected.

3.2 Hand Hygiene

Personnel must perform hand hygiene when entering the compounding area to compound as described in *Box 3-1*. Alcohol hand sanitizers alone are not sufficient.

Box 3-1. Hand Hygiene Procedures

- Wash hands and forearms up to the elbows with soap and water for at least 30 seconds.
- Dry hands and forearms to the elbows completely with disposable towels or wipers.
- Allow hands and forearms to dry thoroughly before donning 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 with 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 and facial hair covers, face masks, gowns) should be worn as needed for the protection of personnel from chemical exposures and for prevention of preparation contamination and must be appropriate for the type of compounding performed. The garbing requirements and frequency of changing the garb must be determined by the facility and documented in the facility's SOPs.

Garb must be stored in a manner that minimizes contamination (e.g., away from sinks to avoid splashing). Visibly soiled garb or garb with tears or punctures must be changed immediately.

If gowns are worn, they may be re-used if not soiled. If used, gloves, shoe covers, hair covers, facial hair covers, face masks, or head coverings may not be re-used and must be replaced with new ones. If used, non-disposable garb, such as goggles, should be cleaned and sanitized with 70% isopropyl alcohol before re-use.

4. BUILDINGS AND FACILITIES

4.1 Compounding Space

Space must be specifically designated for nonsterile compounding. The method of designation (e.g., visible perimeter) must be described in the facility's SOP. Other activities must not be occurring in the space at the same time as compounding. The compounding space must be well-lighted and must be maintained in a clean, orderly, and sanitary condition, and in a good state of repair. Carpet is not allowed in the compounding space. Surfaces should be resistant to damage by cleaning and sanitizing agents.

The space 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 space should be designed, arranged, and used in a way that minimizes cross-contamination from non-compounding areas.

4.2 Storage Area

Compounding personnel must monitor temperatures in storage area(s) 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 for the CNSPs or 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 prevent temperature excursions within 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 and 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 for compounding. The sink must be emptied of all items unrelated to compounding and cleaned when 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⟩), distilled water, or reverse osmosis water should be used for rinsing equipment and utensils.

5. CLEANING AND SANITIZING

Cleaning and sanitizing of 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.

Cleaning and sanitizing agents must be selected and used with consideration of compatibilities, effectiveness, and to minimize the 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 Surfaces in Nonsterile Compounding Area(s)

Site	Minimum Frequency
Work surfaces	• At the beginning and end of each shift, after spills, and when surface contamination is known or suspected • Clean and sanitize the work surfaces between compounding CNSPs with different components
Floors	Daily, after spills, and when surface contamination (e.g., splashes) is known or suspected
Walls	Every 3 months, after spills, and when surface contamination (e.g., splashes) is known or suspected
Ceilings	When visibly soiled and when surface contamination is known or suspected
Storage shelving	Every 3 months, after spills, and when surface contamination (e.g., splashes) is known or suspected

6. EQUIPMENT AND COMPONENTS

6.1 Equipment

The equipment and supplies 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 CNSPs. Disposable or dedicated equipment may be used to reduce the chance of bioburden and cross-contamination.

Equipment must be stored in a manner to minimize the risk of contamination and must be located to facilitate its 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 and 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, conventionally manufactured products] must be assessed to determine if these activities must be performed in 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), or single-use containment glove bags. The process evaluation must be carried out in accordance with the facility SOP and the assessment must be documented.

If a BSC or CVE is used, it must be certified every 12 months according to requirements such as the current Controlled Environment Testing Association (CETA), NSF International, or American Society of Heating, Refrigerating, and Air-Conditioning Engineers (ASHRAE) guidelines, or other laws and regulations of the applicable regulatory jurisdiction.

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

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

Site	Minimum Frequency
CVE	• At the beginning and end of each shift, after spills, and when surface contamination is known or suspected • Clean and sanitize the horizontal work surface of the CVE between compounding CNSPs with different components
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, after 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 APIs and added substances located in the compounding facility. Personnel must be instructed on how to retrieve and interpret needed information.

COMPONENT SELECTION

A designated person 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 the specifications and test results and shows that the API meets the specifications
- In the United States, must be obtained from an FDA-registered facility

- Outside of the United States, must comply with 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 obtained from an FDA-registered facility
    - If it 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 laws and regulations of the applicable regulatory jurisdiction

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 a *USP-NF* monograph, if one exists. For components other than conventionally manufactured products, information including the receipt date, quantity received, supplier name, lot number, expiration date, and results of any in-house or third-party testing performed must be documented.

The date of receipt by the compounding facility must be clearly and indelibly marked on each component package that lacks a vendor expiration date. Packages 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 Components, Component Receipt* if the same component container is also used in sterile compounding or if the ingredient is known to be susceptible to degradation.

For each use, the lot must be examined for evidence of deterioration and other aspects of unacceptable quality. Once removed from the original container, components 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.

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 the other lots have the same defect.

COMPONENT EVALUATION BEFORE USE

Before use, compounding personnel must visually re-inspect all components. Packages must be inspected to detect container breaks, 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 correct identity, strength, purity, and quality of components intended for preparation of CNSPs cannot be confirmed (e.g., containers with damaged or incomplete labeling), they must be immediately rejected. If they are not immediately discarded, they must be clearly labeled as rejected, and segregated to prevent their use before disposal.

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, and quality).

COMPONENT SPILL AND DISPOSAL

The facility must maintain chemical hazard and disposal information (e.g., SDSs) and must review and update its chemical hazard and disposal information every 12 months. The chemical hazard and disposal information (e.g., SDSs) must be made accessible to compounding personnel.

The facility must have an SOP for the management of nonhazardous component spills and disposal. If required by the SOP, these activities must be documented and corrective action taken.

The facility must have a readily accessible spill kit in the compounding area. The contents of the spill kit should be affixed to the packaging of the spill kit if not readily visible on the manufacturer's label.

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. Refresher training must be conducted every 12 months and documented for all personnel who may be required to clean up a spill.

Waste must be disposed of in accordance to laws and regulations of the applicable regulatory jurisdiction. The disposal of components must comply 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 is a detailed record of procedures that describes how the CNSP is to be prepared. A Master Formulation Record must be created for each unique formulation of a CNSP. CNSPs are prepared according to the Master Formulation Record and the preparation information is documented on a Compounding Record (see *7.2 Creating Compounding Records*). Any changes or alterations to the Master Formulation Record must be approved and documented according to the facility's SOP. *Box 7-1* lists the information that must be included in a Master Formulation Record.

Box 7-1. Master Formulation Records

A Master Formulation Record 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 a description of the compounding steps
- Physical description of the final CNSP
- Assigned beyond-use date (BUD) and storage requirements
- Reference source to support the assigned BUD and storage requirements
- If applicable, calculations to determine and verify quantities and/or concentrations of components and strength or activity of API
- 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 documents the compounding of each CNSP. A Compounding Record must be created for all CNSPs. Each Compounding Record must be reviewed for completeness before the CNSP is released. The identifier of the person completing the review and the date of review must be documented on the Compounding Record. The Compounding Record must permit traceability of all components in the case of a recall or known quality issue. The Master Formulation Record can be used as the basis for preparing the Compounding Record. For example, a copy of the Master Formulation Record can be made that contains spaces to record the information needed to complete the Compounding Record. *Box 7-2* lists the information that must be included in a Compounding Record.

Box 7-2. Compounding Records

Compounding Records must include at least the following information:

- Name, strength or activity, and dosage form of the CNSP
- 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 verifying the final CNSP
- Name, vendor or manufacturer, lot number, and expiration date of each component
- Weight or measurement of each component
- Total quantity compounded
- Assigned BUD and storage requirements
- If applicable, calculations to determine and verify quantities and/or concentrations of components and strength or activity of API
- Physical description of the final CNSP
- Results of quality control procedures (e.g., pH testing, visual inspection)
- Master Formulation Record reference for the CNSP

8. RELEASE INSPECTIONS

At the completion of compounding and before release and dispensing, the CNSP must be visually inspected to determine whether the physical appearance is as expected. Inspections must also confirm that the CNSP and its labeling match the Compounding Record and the prescription or medication order. Some CNSPs, as noted in their Master Formulation Record, also must be visually checked for certain characteristics (e.g., emulsions must be checked for phase separation). All checks and inspections, and if required, any other tests necessary to ensure the quality of the CNSP must be detailed in the facility's Master Formulation Records. Checks and inspections must be documented. Additional quality assurance (QA) and quality control activities are described in *12. Quality Assurance and Quality Control*. Pre-release inspection also must include a visual inspection of container–closure integrity (e.g., checking for leakage, cracks in the container, or improper seals). CNSPs with observed defects must be immediately discarded, or marked and segregated from acceptable units in a manner that prevents them from being released or dispensed.

9. LABELING

The term labeling designates all labels and other written, printed, or graphic matter on the immediate container or on, or in, any package 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⟩.

Every dispensed CNSP must be labeled with adequate, legible identifying information to prevent errors during storage, dispensing, and use. All labeling must be in compliance with laws and regulations of the applicable regulatory jurisdiction.

The label on each immediate container of the CNSP must, at a minimum, display the following information:

- Assigned internal identification number (e.g., barcode, prescription, order, or lot number)
- Active component(s), and amounts, activities, or concentrations
- Dosage form
- Amount or volume in each container
- Storage conditions if other than controlled room temperature
- BUD

The labeling on the CNSP should display the following information:

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

Labeling operations must be controlled to prevent labeling errors and CNSP mix-ups. A final check must be conducted to verify that the correct label has been affixed to the finished CNSP. All labels must also comply with laws and regulations of the applicable regulatory jurisdiction.

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 drug product, active ingredient, 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 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 *Labeling* ⟨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 for a particular formulation in its container and at stated exposure conditions of illumination and temperature.

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, it is critical that personnel carefully consider the possible ways that the physical or chemical characteristics of the CNSP could change over time. The following factors must be considered:

- The 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 degrade over time and/or under certain storage conditions, which would reduce the strength of the preparation and/or produce harmful impurities)
- The 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
- The potential for microbial proliferation in the CNSP

10.3 Establishing a BUD for a CNSP

The BUDs indicate the days after the CNSP is prepared and beyond which the CNSP must not be used. The day that the preparation is compounded is considered Day 1. The BUDs in *Table 3* are based on the ability of the CNSP to maintain chemical and physical stability and to suppress microbial growth. *Table 3* represents the maximum BUDs for CNSPs that are packaged in tight, light-resistant containers unless conditions under *10.4 CNSPs Requiring Shorter BUDs* or *10.5 Extending BUDs for CNSPs* apply.

The aqueous and nonaqueous dosage forms in *Table 3* are defined based on the water activity (Aw) of the most similar drug product described in *Application of Water Activity Determination to Nonsterile Pharmaceutical Products* ⟨1112⟩. In general,

the use of Aw aids in assessing the susceptibility of CNSPs to microbial contamination and the potential for API degradation due to hydrolysis. Reduced Aw greatly assists in the prevention of microbial proliferation in conventionally manufactured products and is expected to convey the same benefit to CNSPs. The list of manufactured products in *Application of Water Activity Determination to Nonsterile Pharmaceutical Products* ⟨1112⟩, *Table 2* is not exhaustive. However, it provides guidance on the Aw value of a particular CNSP and can assist personnel in determining the BUD by dosage form based on *Table 3*.

CNSPs with an Aw > 0.6 should contain suitable antimicrobial agents to protect against bacteria, yeast, and mold contamination from proliferation if inadvertently introduced during or after the compounding process. When antimicrobial preservatives are clinically 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. Maximum BUD by Type of Preparation in the Absence of a *USP-NF* Compounded Preparation Monograph or CNSP-Specific Stability Information

Type of Preparation	BUDs (days)	Storage Temperature[a]
Non-preserved aqueous dosage forms[b]	14	Refrigerator
Preserved aqueous dosage forms[b]	35	Controlled room temperature or refrigerator
Nonaqueous dosage forms[c]	90	Controlled room temperature or refrigerator
Solid dosage forms[d]	180	Controlled room temperature or refrigerator

[a] See *Packaging and Storage Requirements* ⟨659⟩.
[b] An aqueous preparation is one that has an Aw of > 0.6 (e.g., emulsions, gels, creams, solutions, sprays, or suspensions).
[c] Any preparation other than solid dosage forms that have a reduced Aw of ≤0.6 (e.g., suppositories, ointments, fixed oils, or waxes).
[d] Capsules, tablets, granules, powders.

10.4 CNSPs Requiring Shorter BUDs

A shorter BUD must be established under the following circumstances:

- If the API or any other components in the CNSP have an expiration date that is earlier than the BUD that could be assigned from *Table 3*, the expiration date supersedes the BUD and must be the assigned shortest date
- If the CNSP includes components from conventionally manufactured product(s), the BUD of the CNSP must not exceed the shortest remaining expiration date of any of those conventionally manufactured product(s)
- If the CNSP includes components from other compounded preparations, the BUD of the final CNSP must not exceed the shortest remaining BUD of any of those compounded preparations
- If the formulation is known to require a shorter BUD

10.5 Extending BUDs for CNSPs

CNSPS WITH A *USP–NF* MONOGRAPH

If there is a *USP–NF* compounded preparation monograph for the CNSP, the BUD must not exceed the BUD specified in the monograph.

CNSPS WITH STABILITY INFORMATION

The BUDs specified in *Table 3* for aqueous dosage forms and nonaqueous dosage forms may be extended up to maximum of 180 days if there is a stability study (published or unpublished) using a stability-indicating assay for the API(s), CNSP, and type of container–closure that will be used.

If the BUD of the CNSP is extended beyond the BUDs in *Table 3*, an aqueous CNSP should be tested for antimicrobial effectiveness (see *Antimicrobial Effectiveness Testing* ⟨51⟩). The compounder may rely on 1) antimicrobial effectiveness testing that is conducted (or contracted for) once for each formulation in the particular container–closure system in which it will be packaged or 2) antimicrobial effectiveness testing results provided by an FDA-registered facility or published in peer-reviewed literature sources if the CNSP 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.

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 SOPs and are responsible for ensuring that they are followed.

One or more person(s) must be designated to ensure that 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 and quality control programs are necessary to ensure that consistently high-quality CNSPs are prepared. 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 CNSP. See *Quality Assurance in Pharmaceutical Compounding* ⟨1163⟩.

A facility's QA and QC programs must be formally established and documented in SOPs that ensure that all aspects of the preparation of CNSPs are conducted in accordance with this chapter and laws and regulations of the applicable regulatory jurisdiction. 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
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. 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.

13. CNSP PACKAGING AND TRANSPORTING

13.1 Packaging of CNSPs

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 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. COMPLAINT HANDLING AND ADVERSE EVENT REPORTING

Compounding facilities must develop and implement SOPs for complaint and adverse event report receipt, acknowledgment, and handling and designate one or more person(s) to be responsible for handling them. Complaints may include concerns or reports on the quality and labeling of, or possible adverse reactions to, a specific CNSP.

14.1 Complaint Handling

The designated person(s) must ensure that all complaints are reviewed 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., e-mail, telephone, mail). The record must contain the name of the complainant or 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, the prescription or medication order number, and the lot number, if one is assigned.

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 *15. 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.

14.2 Adverse Event Reporting

The designated person(s) must ensure that reports of potential adverse events involving a CNSP are reviewed. 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. The designated person(s) must review all adverse event reports as part of the QA and QC programs (see *12. Quality Assurance and Quality Control*). Adverse events must be reported in accordance with facility SOPs and all laws and regulations of the applicable regulatory jurisdiction. In addition, adverse events associated

with a CNSP should be reported to the FDA through the MedWatch program for human drugs and through Form FDA 1932a for animal drugs.

15. 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 corrective actions for any failures
- Equipment records (e.g., calibration, verification, and maintenance reports)
- COA
- Receipt of components
- SOPs, Master Formulation Records, and Compounding Records
- Release inspection and testing records
- Information related to complaints and adverse events including corrective actions taken
- Results of investigation 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 compounding records for a particular CNSP (e.g., Master Formulation Record, Compounding Record, and release inspection and testing results) must be readily retrievable for at least 3 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 and animals or affecting the structure and function of the body.

Added substances: Ingredients that are necessary to compound a preparation but are 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 ingredients, excipients, and pharmaceutical ingredients.

Biological safety cabinet (BSC): A ventilated cabinet which may be used for compounding. These cabinets 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).

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 soil (e.g., organic and inorganic material) from objects and surfaces, normally accomplished by manually or mechanically using water with detergents or enzymatic products.

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

Compounded nonsterile preparation (CNSP): A preparation intended to be nonsterile created by combining, admixing, diluting, pooling, reconstituting other than as provided in the manufacturer's labeling, or otherwise altering of a drug or bulk drug substance.

Compounder: Personnel trained to compound preparations.

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

Compounding area: A space that is specifically designated for nonsterile compounding. A visible perimeter should establish the boundaries of the nonsterile compounding area.

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 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 FDA-approved application 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 for the preparation of CNSPs.

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. See ⟨800⟩.

Label: A display of written, printed, or graphic matter on the immediate container of any article.

Labeling: All labels and other written, printed, or graphic matter that are 1) on any article or any of its containers or wrappers, or 2) accompanying such an article.

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 EU, 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 *Water for Pharmaceutical Purposes* ⟨1231⟩*, 3. Waters Used for Pharmaceutical Manufacturing and Testing Purposes, 3.1 Bulk Monographed Waters and Steam, 3.1.1 Purified Water*.)

Preservative: A substance added to inhibit microbial growth.

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 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 all forms of microbial life including fungi, viruses, and bacteria.

Specification: The tests, analytical methods, and acceptance criteria to which an API or other components, CNSP, container–closure system, equipment, or other material used in compounding 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.

APPENDIX

Acronyms

API(s)	Active pharmaceutical ingredient(s)
ASHRAE	American Society of Heating, Refrigerating, and Air-Conditioning Engineers
Aw	Water activity
BSC(s)	Biological safety cabinet(s)
BUD(s)	Beyond-use date(s)
CETA	Controlled Environment Testing Association
CNSP(s)	Compounded nonsterile preparation(s)
COA	Certificate(s) of Analysis
CVE	Containment ventilated enclosure
FDA	Food and Drug Administration
HD(s)	Hazardous drug(s)
QA	Quality assurance
QC	Quality control
SDS(s)	Safety Data Sheet(s)
SOP(s)	Standard operating procedure(s)▲ USP 1-Dec-2019

2019

USP General Chapter <797> *Pharmaceutical Compounding – Sterile Preparations*

Reprinted from USP 42—NF 37

Links for Supplemental Resources

- Information on USP General Chapter <797>
- USP General Chapter <797> FAQs
- USP General Chapter <797> Education Courses
- Sign up for USP Updates

This text is a courtesy copy of General Chapter <797> Pharmaceutical Compounding – Sterile Preparations, intended to be used as an informational tool and resource only. Please refer to the current edition of the USP-NF for official text.

This chapter alone is not sufficient for a comprehensive approach to pharmaceutical compounding – sterile preparations. Additional chapters are required for complete implementation; see USP Compounding Compendium or USP-NF.

⟨797⟩ PHARMACEUTICAL COMPOUNDING—STERILE PREPARATIONS

Change to read:

▲TABLE OF CONTENTS

1. INTRODUCTION AND SCOPE

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

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 technique must be followed for preparing any sterile medication. 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.

Pursuant to *General Notices, 2.30 Legal Recognition*, assuring compliance with *USP* standards is the responsibility of regulatory bodies. Accreditation or credentialing organizations may adopt and enforce *USP* standards. USP has no role in enforcement.

1.1 Scope

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
- 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

SPECIFIC PRACTICES

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.

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 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 the requirements in this chapter that are applicable to other sterile CSPs. The standards for compounding allergenic extracts are in *21. Compounding Allergenic Extracts* and 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

Otherwise, compounding of allergenic extracts prescription sets must meet the requirements for Category 1 or Category 2 CSPs, which are described in this chapter.

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

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) in order to avoid any cross-contamination. Handling of blood components must additionally comply with jurisdictional standards and guidelines.

Sterile radiopharmaceuticals: Compounding of radiopharmaceuticals is not required to meet the standards of this chapter for Category 1 and Category 2 CSPs and is subject to the requirements in *Radiopharmaceuticals—Preparation, Compounding, Dispensing, and Repackaging* ⟨825⟩.

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 physicians' or veterinarians' practice sites. Any person, whether preparing a CSP or not, entering a sterile compounding area 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 medication to a single patient by injecting, infusing, or otherwise providing a sterile medication 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's (CDC's) safe injection practices apply to administration.

1.3 Immediate Use CSPs

Compounding of CSPs for direct and immediate administration to a patient is not subject to the requirements for Category 1 or Category 2 CSPs when all of the following are met:

1. Aseptic processes are followed and written procedures 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. The preparation is performed in accordance with evidence-based information for physical and chemical compatibility of the drugs (e.g., FDA-approved labeling, stability studies).
3. The preparation involves not more than 3 different sterile products.
4. Any unused starting component from a single-dose container must be discarded after preparation for the individual patient is complete. Single-dose containers must not be used for more than 1 patient.
5. Administration begins within 4 hours following the start of preparation. If administration has not begun within 4 hours following the start of preparation, it must be promptly, appropriately, and safely discarded.
6. Unless 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 exact 4-hour time period within which administration must begin.

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 provided by the product's manufacturer and other manufacturer directions consistent with that labeling [21 USC 353a (e)].

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.

PROPRIETARY BAG AND VIAL SYSTEMS

Docking and activation of proprietary bag and vial systems (e.g., addEASE, ADD-Vantage, Mini Bag Plus) 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) 5 environment.

Docking of the proprietary bag and vial systems for *future activation* and administration is considered compounding and must be performed 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 two categories of CSPs, Category 1 and Category 2, primarily based on the conditions under which they are made, the probability for microbial growth, and the time period within which they must be used. Category 1 CSPs are those assigned a BUD of 12 hours or less at controlled room temperature or 24 hours or less when refrigerated if made in accordance with all of the applicable requirements for Category 1 CSPs in this chapter. Category 2 CSPs are those that may be assigned a BUD of greater than 12 hours at controlled room temperature or greater than 24 hours if refrigerated (see *14. Establishing Beyond-Use Dates*) if made in accordance with all of the applicable requirements for Category 2 CSPs in this chapter.

The requirements that are not specifically described as applicable to Category 1 or Category 2, such as training, competency testing, and personal hygiene for personnel, are applicable to the compounding of all CSPs.

CSPs can be compounded either by using only sterile starting ingredients or by using some or all nonsterile starting ingredients. If all of the components used to compound a drug are sterile to begin with, 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 maintained if the CSP is subsequently manipulated. When compounding with nonsterile starting components, supplies, or equipment, the quality of the components and the effectiveness of the sterilization step are critical to achieving a sterile preparation.

2. PERSONNEL TRAINING AND EVALUATION

All personnel involved in the compounding of CSPs must be initially trained and qualified by demonstrating proficiency in compounding CSPs. A designated person must oversee the training of personnel. Training and observation may be performed by the designated person(s) or an assigned trainer. Personnel must complete training every 12 months in appropriate sterile compounding principles and practices.

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 involved in preparing CSPs. This program should

equip personnel with the appropriate knowledge and train them in the required skills necessary to perform their assigned tasks. Training and evaluation of personnel must be documented.

2.1 Demonstrating Proficiency in Core Competencies

Before beginning to prepare CSPs independently, all compounding personnel must complete training and be able to demonstrate knowledge of principles and proficiency of skills for performing sterile manipulations and achieving and maintaining appropriate environmental conditions. Competency must be demonstrated 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
- 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 primary engineering controls (PECs)
- Principles of movement of materials and personnel within the compounding area

All compounding personnel must complete written or electronic testing every 12 months. Any other personnel handling CSPs and/or accessing the compounding area must complete training and demonstrate competency in maintaining the quality of the environment in which they are performing their assigned task. The designated person(s) must ensure that any person who enters the sterile compounding area maintains the quality of the environment.

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

All compounding personnel must be visually observed initially and every 6 months while performing hand hygiene and garbing procedures (see *3. Personal Hygiene and Garbing*). The visual audit must be documented and the documentation maintained to provide a record of personnel competency.

Initial gloved fingertip and thumb sampling evaluates a compounder's competency in correctly performing hand hygiene and garbing (see *Box 2-1*). Before being allowed to independently compound, all compounders must successfully complete an initial competency evaluation, including visual observation and gloved fingertip and thumb sampling on both hands, no fewer than 3 separate times. Each fingertip and thumb evaluation must occur after performing a separate and complete hand hygiene and full garbing procedure. After the initial competency evaluation, compounding personnel must successfully complete gloved fingertip and thumb sampling at least every 6 months after completing the media-fill test (see *2.3 Competency Testing in Aseptic Manipulation*).

Initial gloved fingertip and thumb sampling must be performed on donned sterile gloves in a classified area or segregated compounding area (SCA). Subsequent gloved fingertip and thumb sampling must be performed on donned sterile gloves 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) sleeves.

Successful completion of initial gloved fingertip and thumb sampling is defined as zero colony-forming units (cfu). Successful completion of subsequent gloved fingertip and thumb sampling after media-fill testing is defined as ≤3 cfu (total from both hands). Action levels for gloved fingertip and thumb sampling results are shown in *Table 1*.

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/time, media and components used including manufacturer, expiration date and lot number, starting temperature for each interval of incubation, dates of incubation, the results, and the identification of the observer and the person who reads and documents the results.

Box 2-1. Gloved Fingertip and Thumb Sampling Procedures

- Use one sampling device per hand (e.g., plates, paddles, or slides) 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 sampling device with a personnel identifier, whether it was from the 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 sampling device because this could cause a false-negative result.
- Using a separate sampling device for each hand, collect samples from all gloved fingers and thumbs from both hands by rolling finger pads and thumb pad over the agar surface.
- Incubate the sampling device at a temperature of 30°–35° for no less than 48 hours and then at 20°–25° for no less than 5 additional days. Store media devices during incubation to prevent condensate from dropping onto the agar 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.

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

Gloved Fingertip and Thumb Sampling	Action Levels (total number of cfu from both hands)
Initial sampling after garbing	>0
Subsequent sampling after media-fill testing (every 6 months)	>3

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

2.3 Competency Testing in Aseptic Manipulation

All compounding personnel must perform media-fill testing to assess their sterile technique and related practices (see *Box 2-2*) initially and every 6 months thereafter. Gloved fingertip and thumb sampling must be performed inside of an ISO Class 5 PEC following media-fill tests to evaluate the ability of the compounder to demonstrate acceptable aseptic processing.

When performing a media-fill test, simulate the most difficult and challenging compounding procedures and processing conditions encountered by the person replacing all the components used in the CSPs with soybean–casein digest media.

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 before 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.

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/time, media and components used including manufacturer, expiration date and lot number, starting temperature for each interval of incubation, dates of incubation, the results, and the identification of the observer and the person who reads and documents the results.

Box 2-2. 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, 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.
- Once the compounding simulation is completed and the final containers are filled with the test media, incubate them 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 media in one or more container–closure unit(s) on or before 14 days.

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.[1, 2] 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 infection) must report these conditions to the designated person(s).

[1] Agalloco J, Akers JE. Aseptic processing: a vision of the future. *Pharm Technol*. 2005; Aseptic Processing supplement, s16.
[2] Eaton T. Microbial risk assessment for aseptically prepared products. *Am Pharm Rev*. 2005;8(5):46–51.

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 CSP and the environment.

3.1 Personnel Preparation

Individuals entering a compounding area must take appropriate steps to minimize microbial contamination of the environment and the CSPs, including hand hygiene (*3.2 Hand Hygiene*), garbing (*3.3 Garbing Requirements*), and consideration of needed materials to be brought into the compounding area. Before entering a compounding area, individuals must remove any items that are not easily cleanable or that 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 as long as the quality of the CSP and environment will not be affected.

3.2 Hand Hygiene

Personnel must wash hands and forearms up to the elbows with soap and water before initiating compounding activities *Box 3-1*). Brushes must not be used for hand hygiene. Hand dryers must not be used. A closed system of soap (i.e., non-refillable container) to minimize the risk of extrinsic contamination must be readily available or in close proximity to the sink.

Box 3-1. Hand Washing Procedures

- Remove visible debris from 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 seconds.
- Dry hands and forearms 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 SOP. Hands must be sanitized with alcohol-based hand rub before donning sterile gloves (see *Box 3-2*). Sterile gloves must be donned in a classified room or SCA.

Box 3-2. Hand Sanitizing Procedures

- Apply an alcohol-based hand rub to dry skin following the manufacturer's instructions for the volume of product to use.
- 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 must be properly garbed in accordance with the facility's SOPs. Garb must be donned and doffed in an order that reduces the risk of contamination. The order of garbing must be determined by the facility and documented in the facility's SOP. Sterile gloves must be donned in a classified room or SCA. 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 ante-room or the SCA at the same time. The minimum garbing requirements include:

- Low-lint garment with sleeves that fit snugly around the wrists and that is enclosed at the neck (e.g., gowns or coveralls)
- Low-lint, disposable covers for shoes
- Low-lint, disposable covers for head that cover the hair and ears, and if applicable, disposable cover for facial hair
- Face mask
- Sterile powder-free gloves
- If using a RABS, such as a CAI or CACI, disposable gloves (e.g., cotton, nonsterile, sterile) should be worn inside gloves attached to the RABS sleeves. Sterile gloves must be worn over 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). When personnel exit

the compounding area, garb except for gowns cannot be reused and must be discarded. Gowns may be re-used within the same shift if the gown is maintained in a classified area or inside the perimeter of an SCA.

If compounding a 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 regularly throughout the compounding process and whenever nonsterile surfaces (e.g., vials, counter tops, chairs, or carts) are touched.

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 gauntlet sleeves and gloves should be changed per the manufacturer's recommendations and as defined in the facility's SOP.

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 ante-room, buffer room, and SCA must be separated from areas not directly related to compounding. The ante-room 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 equipment, supplies, and components to maintain and facilitate 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.

AIR QUALITY STANDARDS

The ISO standards for air quality in controlled environments are provided in *Table 2* and referenced throughout this chapter.

Table 2. ISO Classification of Particulate Matter in Room Air[a]

ISO Class	Particle Count[b] /m³
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.

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 2*) include ante-rooms, buffer rooms, and PECs.

- Ante-rooms providing access to positive pressure buffer rooms must meet at least ISO Class 8 classification. Ante-rooms 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 ante-room. Ante-rooms 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 and Category 2 CSPs must be prepared 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 below 60% to minimize the risk for microbial proliferation and 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 humidifiers/dehumidifiers and air conditioners must not be used within the classified area or within the perimeter of 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.

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 ante-room 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. Air supplied to the cleanroom suite must be introduced through HEPA filters that are located in the ceiling of the buffer and ante-rooms.

Air returns in the cleanroom suite must be low on the wall unless a visual smoke study demonstrates an absence of stagnant airflow where particulate will accumulate. This smoke study along with environmental monitoring must be repeated whenever a change to the placement of equipment within the room is made 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 classified rooms 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 dirty side. Alternatively, facilities may be designed with two separate ante-rooms, a clean ante-room and a dirty ante-room. The ante-room is entered through the dirty side/room, and the clean side/room is the area closest to the buffer room. Required garb must be donned prior to entering the clean side/room of the ante-room (see *3. Personal Hygiene and Garbing*).

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 room to 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 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). If a pass-through 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 and ante-rooms. Access doors should be hands-free. Tacky mats must not be placed within ISO-classified areas.

Segregated compounding area (SCA): A PEC may be located within an unclassified area, without an ante-room or buffer room. This type of design is called an SCA. Only Category 1 CSPs can 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. A visible perimeter must establish the boundaries of the SCA.

THE CSP COMPOUNDING ENVIRONMENT

The PEC must be certified to meet ISO Class 5 or better conditions (see *Table 2*) during dynamic operating conditions and must be designed to prevent 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.

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 3* 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 prevent 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: Examples of LAFS include LAFWs, integrated vertical laminar flow zones (IVLFZs), and biological safety cabinets (BSCs).

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 work tables and 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—A 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 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 ante-room. 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 that generally are not to be opened during compounding operations.

Types of RABS: Examples of RABS include CAIs and 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 (CAI): 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 (CACI): 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 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 ante-room. 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 CSPs, the pharmaceutical isolator must be placed in an ISO Class 8 or better room. [NOTE—An ante-room 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 into the facility and 2) compounders understand how to utilize the unidirectional airflow to maintain first air in the work zone. For placement of a pharmaceutical isolator used for the preparation of HDs, see ⟨800⟩.

Table 3. Summary of Minimum Requirements for Placement of PEC for Compounding Non-HD CSPs[a]

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

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

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

AIR EXCHANGE REQUIREMENTS

For cleanroom suites, adequate HEPA-filtered airflow to the buffer room(s) and ante-room(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 particulates that may be generated from activities and processes in the area
- the equipment located in the room
- the room pressure
- the effects of temperature

See *Table 4* for a summary of ACPH requirements for non-HD sterile compounding areas.

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, 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
- 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 4. 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

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 each ISO classified area (e.g., between the buffer room and ante-room). The pressure differential between the ante-room 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.

FACILITIES PREPARING CSPS FROM NONSTERILE STARTING INGREDIENT(S) OR COMPONENT(S)

Weighing, measuring, or otherwise manipulating components could generate airborne chemical particles (e.g., API, added substances). If preparing a Category 2 CSP from nonsterile component(s), presterilization procedures, such as weighing and mixing, must be completed in no worse than an ISO Class 8 environment (e.g., ante-room, buffer room). Presterilization procedures must be performed in single-use containment glove bags, containment ventilated enclosure (CVE) , BSC, or CACI to minimize the risk of airborne contamination. CVE, BSC, or CACI 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

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 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, sporicidal agents, 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.

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 by cleaning agents, disinfectants, sporicidal agents, 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 sink(s) must be cleaned and disinfected at least daily and a sporicidal agent must be applied at least monthly (see *7.1 Cleaning, Disinfecting,*

and Sporicidal Agents). If compounding is not performed daily, cleaning and disinfecting of the sink must be completed before initiating compounding.

In facilities with a cleanroom suite, 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 dirty side of the ante-room. [NOTE—The order of hand washing and garbing depends on the placement of the sink (see *3.2 Hand Hygiene*).] The buffer room 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 should be recessed and covered, and the covers should be easily cleanable.

In a facility with an SCA design, the sink must be accessible but located at least 1 meter away from the PEC. The sink must not be located inside the perimeter of 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 ante-room 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 an 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 inside the perimeter of the SCA.

5. CERTIFICATION AND RECERTIFICATION

Before a compounding area is used to compound either Category 1 or Category 2 CSPs, it must be certified using procedures in the current Controlled Environment Testing Association (CETA) certification guide for *Sterile Compounding Facilities* or an equivalent guideline. Certification indicates that the compounding area is meeting its design and air quality specifications (see *Table 2*). It is important to place special emphasis on certifying the ISO Class 5 areas.

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 and volume, the 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

It is imperative that all engineering control equipment function as designed and that the levels of total airborne particles remain within acceptable limits during compounding (see *Table 2*). A monitoring program for total airborne particles must be developed and implemented 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 count testing must be conducted in all classified areas during dynamic operating conditions at least every 6 months.

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 SOP. Measurements of total airborne particles in other classified areas, including the buffer room(s) and ante-room(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 2* 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 2*, *Table 5*, and *Table 6*).

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 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 must 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 in the proper operation of the air and surface sampling equipment to ensure accurate and reproducible sampling. All active 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 using an impaction device 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 at least every 6 months. Air sampling sites must be selected in all classified areas.

SAMPLING PROCEDURES

When conducting sampling of the PEC, care should be taken to avoid disturbing unidirectional airflow. See *Box 6-1* 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 media meets the expected growth promotion, pH, and sterilization requirements. Samples must be incubated in an incubator at temperatures that will promote growth of bacteria and fungi. 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 6-1. Active Air Sampling Procedures for Viable Airborne Monitoring

- Follow the manufacturer's instructions for operation of the active air sampling device, including placement of media.
- Using the sampling device, test at least 1 cubic meter or 1000 liters of air from each location sampled.
- At the end of the sampling, retrieve the media devices and cover them.
- 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 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.
- Then incubate the inverted media at 20°–25° for no less than 5 additional days. Examine the media devices 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.
- 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.
    - If fungal media are used as one of the samples, incubate the fungal media sample 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 cubic meter of air.
  - 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.

DATA EVALUATION AND ACTION LEVELS

Evaluate cfu counts against the action levels in *Table 5*, and examine counts in relation to previous data to identify adverse results or trends. If two devices of media are collected at a single location, all recovered growth on each must be documented and action levels applied to each media device. If levels measured during the viable air monitoring program exceed the levels in *Table 5* 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 viable air sampling exceed the levels in *Table 5*, 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 5. Action Levels for Viable Airborne Particle Air Sampling[a]

ISO Class	Air Sampling Action Levels [cfu per cubic meter (1000 liters) of air per plate]
5	>1

Table 5. Action Levels for Viable Airborne Particle Air Sampling[a] *(continued)*

ISO Class	Air Sampling Action Levels [cfu per cubic meter (1000 liters) of air per plate]
7	>10
8	>100

[a] Adapted from *Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice*. U.S. Department of Health and Human Services, FDA, September 2004.

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 of component and/or vial surfaces. 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 pass-through chambers connecting to classified areas for microbial contamination must be conducted at least monthly (see *Microbiological Control and Monitoring of Aseptic Processing Environments* ⟨1116⟩). Each classified area must be sampled, including the following:

- The interior of the PEC and the equipment contained in it
- Staging or work area(s) near the PEC
- Frequently touched surfaces

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

SAMPLING PROCEDURES

See *Box 6-2* for the procedures for surface sampling on flat surfaces. 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 devices 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. Surface sampling 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 Agents in Compounding Areas*).

Samples must be incubated in a calibrated incubator at temperatures that will promote growth of bacteria and fungi. 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 6-2. Surface Sampling Procedures

- Remove the cover from the surface sampling device. Using a rolling motion, firmly press the media surface onto the surface to be sampled. The surface sampling device will leave a residue of growth media on the sample site. After sampling, remove the residue from the surface using sterile 70% IPA.
- Cover each surface sampling device. Store media devices during incubation to prevent condensate from dropping onto the agar and affecting the accuracy of the cfu reading (e.g., invert plates).
- 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 device as cfu per sample on an environmental sampling form based on sample type (i.e., surface), sample location, and sample date.
- Incubate the surface sampling device at 20°–25° for no less than 5 additional days. Examine the device 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.
- 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., MEA or 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.
    - If fungal media are used as one of the samples, incubate the fungal media sample 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., surface), and include the sample location, and sample date.

DATA EVALUATION AND ACTION LEVELS

Evaluate cfu counts against the action levels in *Table 6*, 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 device of media. If levels measured during surface sampling exceed the levels in *Table 6* 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 6*, an attempt must be made to identify any microorganism recovered to the genus level (see ⟨1113⟩) with the assistance of a microbiologist.

Table 6. Action Levels for Surface Sampling

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

7. CLEANING, DISINFECTING, AND APPLYING SPORICIDAL AGENTS IN COMPOUNDING AREAS

Cleaning, disinfecting, and applying a sporicidal agent are important because surfaces in classified areas and SCA 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.

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. A sporicidal agent must be applied to destroy bacterial and fungal spores. Some EPA-registered (or equivalent) one-step disinfectant cleaners may have sporicidal properties. After cleaning and disinfecting or the application of a one-step disinfectant cleaner, or the application of a sporicidal agent in a PEC, apply sterile 70% IPA to remove any residue. See *Table 7* for a summary of the purposes of the cleaning, disinfectant, and sporicidal agents.

Table 7. Purpose of Cleaning, Disinfecting, and Sporicidal Agents

Type of Agent	Purpose
Cleaning agent	An agent used for the removal of residues (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 agent	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.

Cleaning and disinfecting surfaces and applying a sporicidal agent must occur at the minimum frequencies specified in *Table 8* or, if compounding is not performed daily, cleaning and disinfecting must be completed before initiating compounding.

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 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, and must be followed by all cleaning personnel. The manufacturer's directions 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 8. Minimum Frequency for Cleaning and Disinfecting Surfaces and Applying Sporicidal Agents in Classified Areas and within the Perimeter of the SCA[a]

Site	Cleaning	Disinfecting	Applying Sporicidal
PEC(s) and equipment inside the PEC(s)	Equipment and all interior surfaces of the PEC daily and when surface contamination is known or suspected.	• Equipment and all interior surfaces of the PEC daily and when surface contamination is known or suspected. • Apply sterile 70% IPA to the horizontal work surface at least every 30 minutes if the compounding process takes 30 minutes or less. If the compounding process takes more than 30 minutes, compounding must not be disrupted and the work surface of the PEC must be disinfected immediately after compounding.	Monthly
Removable work tray of the PEC	• Work surface of the tray daily • All surfaces and the area underneath the work tray monthly	• Work surface of the tray daily • All surfaces and the area underneath the work tray monthly	• Work surface of the tray monthly • All surfaces and the area underneath the work tray monthly
Pass-through(s)	Daily	Daily[b]	Monthly
Work surface(s) outside the PEC	Daily	Daily[b]	Monthly
Floor(s)	Daily	Daily[b]	Monthly
Wall(s), door(s), and door frame(s)	Monthly	Monthly[b]	Monthly
Ceiling(s)[c]	Monthly	Monthly[b]	Monthly
Storage shelving and bins	Monthly	Monthly[b]	Monthly
Equipment outside the PEC(s)	Monthly	Monthly[b]	Monthly

[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 agent only when visibly soiled and when surface contamination is known or suspected.

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 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 agent is applied to the surface, the agent must be allowed to dwell for the minimum contact time specified by the manufacturer.

7.2 Cleaning Supplies

All cleaning supplies (e.g., wipers, sponges, and mop heads) with the exception of tool handles and holders must be low-lint. Wipers, 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., 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 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. Dispose of cleaning supplies used in the classified areas and SCAs in a manner that minimizes the potential for dispersing contaminants into the air (e.g., with minimal agitation, away from work surfaces).

7.3 Cleaning, Disinfecting, and Applying Sporicidal Agents in the PEC

Clean, disinfect, and apply a sporicidal agent to equipment and all interior surfaces in the PEC at the minimum frequencies specified in *Table 8*. See *Box 7-1* and *Box 7-2* for procedures for cleaning, disinfecting, and applying a sporicidal agent in the PEC.

Box 7-1. Procedures for Cleaning and Disinfecting the PEC

- 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 low-lint wiper, apply a cleaning agent, followed by a disinfecting agent, or apply an EPA-registered (or equivalent) 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 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 7-2. Procedures for Applying a Sporicidal Agent in the PEC

- 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 (*Box 7-1*), apply the sporicidal agent using a low-lint wiper to all surfaces and the area underneath the work tray. If the sporicidal agent is an EPA-registered (or equivalent) 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 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 Cleanroom Suite and SCAs

Before any item is introduced into the clean side of ante-room(s), placed into pass-through(s), or brought inside the perimeter SCA and when packaging integrity will not be compromised, it must be wiped with a sporicidal agent, EPA-registered disinfectant, or sterile 70% IPA using low-lint wipers by personnel wearing gloves. If an EPA-registered disinfectant or sporicidal agent 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 must not 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 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 entering or puncturing stoppers/septums or breaking the necks of ampules.

9. EQUIPMENT, SUPPLIES, AND COMPONENTS

9.1 Equipment

PECs are described in *4.2 Facility Design and Environmental Controls, 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 agent, 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.

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 facility SOPs, which must address the selection, receipt, evaluation, handling, storage, and documentation of all CSP components, including all ingredients, containers, and closures.

COMPONENT SELECTION

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

- Must comply with the criteria in the *USP–NF* monograph, if one exists
- Must have a COA that includes the specifications and test results and shows that the API meets the specifications
- Must be obtained from an FDA-registered facility

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
- Should be obtained from an FDA-registered facility
    - If it 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 is 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.

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⟩).

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 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.

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, master formulation record (if used), vendor labels, COAs of API(s) and other component(s), product labeling of conventionally manufactured sterile products, labeling of CSPs, and documentation of the compounding facility storage conditions and practices.

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

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 manufacturer.

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, and quality) or the packaging integrity. See also the ⟨1229⟩ family of chapters.

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

- Terminal sterilization (e.g., dry heat, steam, 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 is not an option when compounding a suspension if the suspended drug particles are removed by the filter being used.

CSPs that are terminally sterilized (e.g., dry heat, steam, 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 hours 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° up to about 400°, depending on the exposure time (e.g., a cycle might hold the items at 250° for 30 minutes 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, temperature). This verification must be documented.

Items that are not thermostable must be depyrogenated by rinsing with sterile, non-pyrogenic water (e.g., *Sterile Water for Injection*, *Sterile Water for Irrigation*) and then thoroughly drained or dried immediately before use in compounding.

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 include labeling for pharmaceutical use. Sterilizing filters with labeling that states "for laboratory use only" or an equivalent 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, if necessary, modified. 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 no 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., between 20 and 60 minutes 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 for steam sterilization that must be wrapped, wrap them in low-lint protective fabric or paper or sealed in envelopes that will permit steam penetration and that are designed to prevent post-sterilization microbial contamination. For CSPs, immediately before filling ampules and vials 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. Deep containers, such as beakers and graduated cylinders, must be inverted or placed on their sides at a downward-sloping angle to minimize air entrapment and to facilitate condensate drainage, or must have a small amount of sterile water placed in them before steam sterilization. Porous materials and those items with occluded pathways (e.g., tubing) must only be sterilized by steam if the autoclave chamber has suitable cycles for dry goods, such as a pre-vacuum process to remove air before steam is sent into the chamber. Elastomeric closures and many other dry goods will need a drying cycle after steam exposure to remove condensed or absorbed moisture.

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 and integrators (see *Physicochemical Integrators and Indicators for Sterilization* ⟨1229.9⟩).

The steam supplied must be free of contaminants and 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 compounding record.

10.4 Sterilization by Dry Heat

Dry heat may be used for those items that cannot be sterilized by steam or other means, when either 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.

Dry heat sterilization is usually performed in an oven designed for sterilization at a temperature of 160° or higher. If lower temperatures are used, they must be shown to achieve effective sterilization (see *Dry Heat Sterilization* ⟨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 compounding record.

11. MASTER FORMULATION AND COMPOUNDING RECORDS

11.1 Creating Master Formulation Records

A Master Formulation Record is a detailed record of procedures that describes how the CSP is to be prepared. A Master Formulation Record must be created for CSPs prepared for more than 1 patient and for CSPs prepared from nonsterile ingredient(s). Any changes or alterations to the Master Formulation Record must be approved and documented according to the facility's SOP. *Box 11-1* lists the information that must be included in a Master Formulation Record.

Box 11-1. Master Formulation Records

A Master Formulation Record must include at least the following information:

- Name, strength or activity, and dosage form of the CSP
- Identities and amounts of all ingredients
- 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 (e.g., steam, dry heat, irradiation, or filter)

11.2 Creating Compounding Records

A Compounding Record documents the compounding of each CSP. A Compounding Record must be created for all CSPs. The Compounding Record must be created to document the compounding process or repackaging process. A prescription or medication order or label may serve as the compounding record. If an ACD, workflow management system, or other similar equipment is used, the required information in the compounding record may be stored electronically as long as it is retrievable and contains the required information (see *Box 11-2*). A Master Formulation Record can serve as the basis for preparing the Compounding Record. For example, a copy of the Master Formulation Record can be made that contains spaces for recording the information needed to complete the Compounding Record. *Box 11-2* lists the information that must be included in a Compounding Record.

Box 11-2. Compounding Records

Compounding Records 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 verifying the final CSP
- Name of each component
- Vendor, lot number, and expiration date for each component for CSPs prepared for more than 1 patient and for CSPs prepared from nonsterile ingredient(s)
- Weight or volume of each component
- Strength or activity of each component
- Total quantity compounded
- Assigned BUD and storage requirements
- Results of QC procedures (e.g., visual inspection, filter integrity testing, pH testing)

If applicable, the Compounding Record must also include:

- Master Formulation Record 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., it is inspected for evidence of inappropriate visible particulates or other foreign matter, discoloration, or other defects). The CSP 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). CSPs with observed

defects must be discarded, or marked and segregated from acceptable units in a manner that prevents them from being released or dispensed.

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. A CSP with such defects must be immediately discarded, or marked and segregated from acceptable units in a manner that prevents it from being released or dispensed. Any defect may indicate sterility or stability problems, which should be investigated to determine the cause (see *18. Quality Assurance and Quality Control*).

12.2 Sterility Testing

Sterility testing is not required for Category 1 CSPs (see *Table 10*). If a Category 2 CSP is assigned a BUD that requires sterility testing (see *Table 11*), the testing must be performed according to ⟨71⟩ or a validated alternative method (see *Validation of Alternative Microbiological Methods* ⟨1223⟩) that is non-inferior to ⟨71⟩ testing.

If sterility testing is performed, the minimum quantity of each container to be tested for each media is specified in *Sterility Tests* ⟨71⟩, *Table 2*, and the number of containers required to be tested in relation to the batch size is specified in *Sterility Tests* ⟨71⟩, *Table 3*, except as described below.

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 *Sterility Tests* ⟨71⟩, *Table 3*, additional units must be compounded to be able to perform sterility testing as follows:

- If between 1 and 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 *Sterility Tests* ⟨71⟩, *Table 3* must be used.

If sterility testing is performed according to ⟨71⟩, a *Sterility Tests* ⟨71⟩*, Method Suitability Test* must be performed to ensure that contamination can be recovered. If performing sterility testing according to ⟨71⟩, the *Sterility Tests* ⟨71⟩*, Test for Sterility of the Product to Be Examined, Membrane Filtration* method 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 2 injectable CSPs made from one or more nonsterile component(s) and assigned a BUD that requires sterility testing (see *Table 11*) must be tested to ensure that they do not contain excessive bacterial endotoxins (see ⟨85⟩). Category 2 injectable CSPs made 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 endotoxins limit in an official monograph or other CSP formula source, the CSP must not exceed the endotoxins limit calculated as described in ⟨85⟩ for the appropriate route of administration for humans. CSPs for non-human species must not exceed the endotoxin reference limits calculated as described in ⟨85⟩ based on the weight of the target animal 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

CSPs must be labeled with 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 in, 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⟩.

The label on the 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 amounts, activities, or concentrations
- Storage conditions if other than controlled room temperature
- BUD
- Route of administration

- 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 should indicate that the preparation is compounded.

If the CSP is to be sent outside of the facility in which it was compounded, the labeling must include the contact information of the compounding facility. The labeling of the CSP must also provide any applicable special handling instructions or warning statements.

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

All labels must also comply with laws and regulations of the applicable regulatory jurisdiction.

14. ESTABLISHING BEYOND-USE DATES

14.1 Terminology

Each CSP label must state the BUD, which is the date, or the hour and date, beyond which the preparation must not be used and must be discarded. The BUD is determined from the date/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 compendial 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 the conventionally manufactured product, API, or added substance may be dispensed or used (see *Labeling ⟨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 for a particular formulation in its container and at stated exposure conditions of illumination and temperature. See *Table 9* for a summary of terms.

Table 9. 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/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 compendial 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

Multiple factors that affect sterility and chemical and physical stability must be considered when establishing BUDs for CSPs. BUDs should be established conservatively for CSPs 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 factors that may affect stability, including but not limited to:

- The chemical and physical properties of the drug and/or its formulation
- The compatibility of the container–closure system with the finished preparation (e.g., leachables, interactions, and storage conditions)

The BUDs for CSPs in *Table 10* and *Table 11* are based primarily on factors that affect the achievement and maintenance of sterility, which include, but are not limited to, the following:

- Environment in which the CSP is prepared (e.g., PEC in a cleanroom suite or SCA)
- Aseptic processing and sterilization method
- Starting components (e.g., sterile or nonsterile starting ingredients)
- Whether or not sterility testing is performed
- Storage conditions (e.g., packaging and temperature)

ASEPTIC PROCESSING AND STERILIZATION METHODS

A CSP may be prepared by the following methods (see *10. Sterilization and Depyrogenation*):

1. **Aseptic processing**, which includes either 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.]
2. **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., dry heat, steam, irradiation).

Terminal sterilization is the preferred method of sterilization, unless the specific CSP or container–closure system cannot tolerate terminal sterilization. *Table 11* allows for longer BUDs for CSPs that are terminally sterilized than for aseptically processing CSPs because terminal sterilization using a verified method provides reasonable assurance that a CSP will be sterile.

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 in *Table 11* for CSPs that are aseptically processed from conventionally manufactured sterile starting component(s) than from one or more nonsterile starting component(s).

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 in *Table 11* if sterility testing results are within acceptable limits.

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 10* and *Table 11* 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 re-frozen.

CSPs may be stored under different storage conditions before they are used (e.g., CSPs may first be frozen, and 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 1 day 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 (i.e., controlled room temperature), the CSP must be used within the time frame for that storage condition (in this example, 1 day).

14.3 Establishing a BUD for a CSP

BUDs for CSPs must be established in accordance with *Table 10* for Category 1 CSPs and *Table 11* for Category 2 CSPs. One day is equivalent to 24 hours.

The BUDs in *Table 10* and *Table 11* for CSPs are based on the risk of microbial contamination or not achieving sterility despite implementation of the requirements in this chapter. Therefore, it is assumed that the CSP formulation will remain chemically and physically stable, and its packaging will 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 *Table 10* or *Table 11*. Additionally, the BUD must not exceed the shortest remaining expiration date or BUD of any of the starting components, regardless of the source.

Table 10 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 10. BUDs for Category 1 CSPs

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

Table 11 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 11. BUDs for Category 2 CSPs

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

14.4 Multiple-Dose CSPs

A compounded multiple-dose container is designed to contain more than 1 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 injections). 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 CSP. A multiple-dose CSP must additionally pass antimicrobial effectiveness testing in accordance with *Antimicrobial Effectiveness Testing* ⟨51⟩. The compounder may rely on 1) antimicrobial effectiveness testing that is conducted (or contracted for) once for each formulation in the particular container–closure system in which it will be packaged or 2) antimicrobial effectiveness testing results provided by an FDA-registered facility or published in peer-reviewed literature sources if 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 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 *Package Integrity Evaluation—Sterile Products* ⟨1207⟩). The container–closure integrity test needs to be conducted only once on each formulation and fill volume in the particular container–closure system in which the multiple-dose CSP will be packaged.

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 medication 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 hours after initial entry or puncture as long as the storage requirements during that 12-hour 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 1 dose of a drug product (see *Packaging and Storage Requirements* ⟨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 *Packaging and Storage Requirements* ⟨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 finished 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 finished CSP(s). The BUD of a CSP prepared from one or more compounded components may not exceed the shortest BUD of any of the individual starting components (see *14. Establishing Beyond-Use Dates*).

16.1 Use of Compounded Multiple-Dose CSPs

A multiple-dose CSP is designed to contain more than 1 dose of medication, 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 *14.4 Multiple-Dose CSPs*. Multiple-dose CSPs must be stored under the conditions upon which its BUD is based (e.g., refrigerator, 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.

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, controlled room temperature). The component CSP may be used for sterile compounding for up to 12 hours or its assigned BUD, whichever is shorter, and any remainder must be discarded.

17. SOPs

Facilities that prepare CSPs must develop SOPs for the compounding process and other support activities. A designated person 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 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 able 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 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 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 SOPs that ensure that all aspects of the preparation of CSPs are conducted in accordance with the requirements in this chapter and laws and regulations of the applicable regulatory jurisdiction. 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

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(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:

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

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 disposition and reconciliation of the recalled CSP

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 (e.g., state board of pharmacy, state health department).

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 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, mail). The record must contain the name of the complainant or 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 facility SOPs and all laws and regulations of the applicable regulatory jurisdiction. In addition, adverse events potentially associated with the quality of the CSP 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, or FDA Form 1932a for animal drugs).

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

Processes and techniques for handling, storing, packaging, and transporting CSPs must be outlined in 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 at least once daily 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 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, Master Formulation Records (when used), and Compounding Records
- Release inspection and testing records
- Information related to complaints and adverse events
- Results of investigations and corrective actions

Documentation must comply with all laws and regulations of the applicable jurisdiction. Records must be legible and stored in a manner that prevents their deterioration and/or loss. All required compounding records for a particular CSP (e.g., Master Formulation Record, Compounding Record, and release testing results) must be readily retrievable for at least 3 years after preparation or as required by laws and regulations of the applicable regulatory jurisdiction, 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)]. Because patients must be maintained on a maintenance dose of prepared concentrated allergenic extracts for a period of time longer than the BUDs specified for Category 1 and Category 2, longer BUDs are required for prescription sets to achieve effective therapy.

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

Personnel Qualifications

1. A designated person with training and expertise in allergen immunotherapy is responsible for ensuring that personnel who will be preparing allergen immunotherapy are trained, evaluated, and supervised.
2. 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.
3. Annual personnel training and competency must be documented. Personnel must demonstrate proficiency in these procedures by passing written or electronic testing before they can be allowed to compound allergenic extract prescription sets.
4. Before being allowed to independently compound, all compounders must successfully complete gloved fingertip and thumb sampling on both hands (see *Box 2-1* 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 procedure. After the initial competency evaluation, compounding personnel must successfully complete gloved fingertip and thumb sampling at least every 12 months thereafter.

5. Compounding personnel must have their sterile technique and related practices evaluated every 12 months as demonstrated by successful completion of a media-fill test (see *Box 2-2*).

6. 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.

7. 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.

Personnel Hygiene and Garbing

8. Before beginning compounding of allergen immunotherapy prescription sets, personnel must perform hand hygiene (see *Box 3-1*) and garbing procedures according to facility SOPs.

9. The minimum garb requirements include:

- Low-lint garment with sleeves that fit snugly around the wrists and that is enclosed at the neck (e.g., gowns or coveralls)
- Low-lint, disposable covers for head that cover the hair and ears and, if applicable, disposable cover for facial hair
- Face mask
- Sterile powder-free gloves

10. Compounding personnel must rub sterile 70% IPA onto all surfaces of the gloves and allow them to dry thoroughly throughout the compounding process.

Facilities

11. The compounding process must occur in an ISO Class 5 PEC or in a dedicated allergenic extracts compounding area (AECA). The PEC or AECA used to compound 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 meter 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 every 6 months (see *5. Certification and Recertification*).
- If used, a visible perimeter must establish the boundaries of 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 sanitizing 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.

Cleaning and Disinfecting

12. In a PEC, all interior surfaces of the PEC must be cleaned and disinfected daily and when surface contamination is known or suspected. Apply sterile 70% IPA to the horizontal work surface between each prescription set.

13. In an AECA, all work surfaces in the AECA where direct compounding is occurring must be cleaned and disinfected daily 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.

14. 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 extracts prescription sets.

Establishing BUDs

15. 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.

Labeling

16. 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

Shipping and Transport

17. 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.

18. When shipping or transporting allergenic extract prescription sets that require special handling, personnel must include specific handling instructions on the exterior of the container.

Documentation

19. 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 the refrigerator(s)
- Compounding records for individual allergenic extract prescription sets (see *Box 21-1*)
- Information related to complaints and adverse events
- Investigations and corrective actions

Box 21-1. Compounding Records for Individual Allergenic Extract Prescription Sets

Compounding Records must include at least the following information:

- Name, concentration, volume, vendor or manufacturer, lot number, and expiration date for each component
- Date and time of preparation of the allergenic extract
- Assigned internal identification number
- A method to identify the individuals involved in the compounding process and verifying the final CSP
- Total quantity compounded
- Assigned BUD and storage requirements
- Results of QC procedures (e.g., visual inspection, second verification of quantities)

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 and animals or affecting the structure and function of the body.

Added substances: Ingredients that are necessary to compound a preparation but are 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 ingredients, excipients, and pharmaceutical ingredients.

Administration: The direct application of a sterile medication to a single patient by injecting, infusing, or otherwise providing a sterile medication 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.

Allergenic extract prescription set: Combinations of licensed allergenic extracts which 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.

Allergenic extracts: Biological substances 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 extracts compounding area (AECA): A designated, unclassified space, area, or room with a visible perimeter that is suitable for preparation of allergenic extract prescription sets.

Ante-room: 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 ante-room 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, 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.

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.

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.

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 ante-room.

Category 1 CSP: A CSP that is assigned a BUD of 12 hours or less at controlled room temperature or 24 hours 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 is assigned a BUD of greater than 12 hours at controlled room temperature or greater than 24 hours refrigerated that is compounded in accordance with all applicable requirements for Category 2 CSPs in this chapter.

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.

Classified area: An area that maintains an air quality classification based on the ISO standards (see also the definition for *ISO class*).

Cleaning agent: An agent for the removal of residues (e.g., dirt, debris, microbes, and residual drugs or chemicals) from surfaces.

Cleanroom suite: A classified area that consists of both an ante-room 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 or bulk drug substance to create a sterile medication.

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.

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 ventilated enclosure: 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.

Conventionally manufactured product: A pharmaceutical dosage form, usually the subject of an FDA-approved application, and 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 compounding facility and personnel in 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 disinfectant agents 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 *Dynamic operating conditions*). This test is not appropriate for ISO Class 7 or ISO Class 8 cleanrooms that do not have unidirectional airflow (see *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).

Excipients: See *Added substances*.

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.

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, coveralls), 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).

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.

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 work tables and effective placement of air returns.

ISO class: An air-quality classification from the International Organization for Standardization.

Laminar airflow system (LAFS): A device or zone within a buffer area 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 ante-room.

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.

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.

Multiple-dose container: A container of sterile medication for parenteral administration (e.g., injection or infusion) that is designed to contain more than 1 dose of the medication. A multiple-dose container is usually required to meet the antimicrobial effectiveness testing criteria. See *Packaging and Storage Requirements* ⟨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 non-porous 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 that should be interlocked. The pass-through is positioned between two spaces for the purpose of minimizing particulate transfer while moving materials from one space to another.

Perimeter: A visible demarcation that defines the boundaries of the SCA or AECA (e.g. a visible line or wall).

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 *Packaging and Storage Requirements* ⟨659⟩*, Injection Packaging Systems, Pharmacy bulk package*.

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.]

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.

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.

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, unclassified space, area, or room with a defined perimeter that contains a PEC and is suitable for preparation of Category 1 CSPs only.

Single-dose containers: A container of sterile medication 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 *Packaging and Storage Requirements* ⟨659⟩*, Injection Packaging Systems, Single-dose container*.

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

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.

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 *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 membranes: 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-µm or 0.2-µm pore size.

Terminal sterilization: The application of a lethal process (e.g., dry heat, steam, 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.

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.

Workflow management system: Technology comprised of hardware and software that allows for automation to assist in the verification of components of, and preparation of, CSPs and to document components and processes.

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 where particulates can accumulate. This test does not need to be performed under dynamic operating conditions and is not appropriate for PECs (see *Dynamic airflow smoke pattern test*).

APPENDIX

Acronyms

ACD	Automated compounding device
ACPH	Air changes per hour
AECA	Allergenic extracts compounding area
APIs	Active pharmaceutical ingredient(s)
BLA	Biological License Application
BMBL	Biosafety in Microbiological and Biomedical Laboratories
BSC(s)	Biological safety cabinet(s)
BUD(s)	Beyond-use date(s)
CACI	Compounding aseptic containment isolator
CAI	Compounding aseptic isolator
CDC	Centers for Disease Control and Prevention
CETA	Controlled Environment Testing Association
cfu	Colony-forming units
COA(s)	Certificate(s) of analysis
CSP(s)	Compounded sterile preparation(s)
CVE	Containment ventilated enclosure
DCA(s)	Direct compounding area(s)
ECV(s)	Endotoxin challenge vial(s)
EPA	Environmental Protection Agency
FDA	Food and Drug Administration
HD(s)	Hazardous drug(s)
HEPA	High-efficiency particulate air
HVAC	Heating, ventilation, and air conditioning

Acronyms *(continued)*

IPA	Isopropyl alcohol
ISO	International Organization for Standardization
IVLFZ	Integrated vertical laminar flow zone
LAFS	Laminar airflow system
LAFW(s)	Laminar airflow workbench(es)
MEA	Malt extract agar
PEC(s)	Primary engineering control(s)
PNSU	Probability of a nonsterile unit
PPE	Personal protective equipment
QA	Quality assurance
QC	Quality control
RABS	Restricted-access barrier system
SAL	Sterility assurance level
SCA	Segregated compounding area
SDA	Sabouraud dextrose agar
SEC(s)	Secondary engineering control(s)
SOP(s)	Standard operating procedure(s)
TSA	Trypticase soy agar▲ USP 1-Dec-2019

2019

USP General Chapter <825> *Radiopharmaceuticals – Preparation, Compounding, Dispensing, and Repackaging*

Reprinted from USP 42—NF 37

Links for Supplemental Resources

- Information on USP General Chapter <825>
- USP General Chapter <825> FAQs
- Sign up for USP updates

This text is a courtesy copy of General Chapter <825> Radiopharmaceuticals – Preparation, Compounding, Dispensing, and Repackaging, intended to be used as an informational tool and resource only. Please refer to the current edition of the USP-NF for official text.

This chapter alone is not sufficient for a comprehensive approach to radiopharmaceuticals – preparation, compounding, dispensing, and repackaging. Additional chapters are required for complete implementation; see USP Compounding Compendium or USP-NF.

Add the following:

▲⟨825⟩ RADIOPHARMACEUTICALS—PREPARATION, COMPOUNDING, DISPENSING, AND REPACKAGING

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/m^3 (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

Table 5. Minimum Frequency for Cleaning and Disinfecting Surfaces in Classified Areas and within the Perimeter of the SRPA *(continued)*

Site	Cleaning	Disinfecting[a]	Applying Sporicidal
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 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.

[1] Centers for Disease Control and Prevention. *Guideline for Disinfection and Sterilization in Healthcare Facilities*, 2008.

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

Abbreviations *(continued)*

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
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▲ USP 1-Dec-2019

Proposal to Rename Article 7 Sterile Compounding and Repeal Sections 1751-1751.10 and Replace as Follows:

Article 7 Sterile Compounding in Pharmacies

1751. Sterile Compounding in Licensed Pharmacies.

This article applies to sterile compounding performed in a pharmacy. A pharmacy performing sterile compounding shall comply with the standards established by United States Pharmacopeia (USP) General Chapter 797 (Chapter 797), titled *Pharmaceutical Compounding – Sterile Preparations*, unless additional or different standards are established by this article.

(a) For purposes of this article, compounding, occurs in a pharmacy, by or under the supervision of a licensed pharmacist, pursuant to a patient specific prescription.

(b) Compounded sterile preparation (CSP) for immediate administration shall only be done in those limited situations where there is a need for immediate administration of a CSP and where failure to administer could result in loss of life or intense suffering. Any such CSP shall be labeled ~~"for immediate use only" and~~ with a beyond use date/time of 4 hours or less. The pharmacy shall maintain records of such CSPs shall at least include CSP made, compounded time, and patient name and patient unique identifier.

(c) Reconstitution in accordance with directions that have not been approved by the FDA, is considered compounding and this article applies.

(d) Except as identified below, ~~No~~ no CSPs shall be compounded prior to receipt by a pharmacy of a valid patient specific prescription document. Where approval is given orally, that approval shall be noted on the prescription document prior to compounding.

(1) ~~Notwithstanding this subdivision, a~~ A pharmacy may prepare and store a limited quantity of a CSP in advance of receipt of a patient specific prescription document.

(2) Notwithstanding this subdivision, a pharmacy may prepare and provide a limited quantity of CSPs to veterinarians for animal patients based on a contract between the pharmacy and veterinarian for office use administration only. The pharmacy and veterinarian practice are jointly responsible for compliance with this section. The contract shall require the veterinarian to provide the pharmacy with the records documenting the dose administered to each patient or destruction record of CSPs. The pharmacy shall be prohibited from providing the same~~additional~~ CSP~~s~~ to the veterinarian until the pharmacy has received and evaluate the records for compliance with this provision.

Commented [SA2]: Clarify additional products or frequency?

(e) No pharmacy or pharmacist shall compound a CSP that:

(1) Is classified by the United States Food and Drug Administration (FDA) as demonstrably difficult to compound;

(2) Appears on an FDA list of drugs which have been withdrawn or removed from the market because such drugs or components of such drug preparations have been found to

be unsafe or not effective; or
(3) Is a copy or essentially a copy of one or more commercially available drug products, unless
(A) that drug product appears on an ASHP (American Society of Health-System Pharmacists) or FDA list of drugs that are in short supply at the time of compounding ~~and at the time of compounding~~ and at the time of dispense, or
(B), the compounding of that CSP is justified by a specific, documented medical need made known to the pharmacist prior to compounding.
The pharmacy shall retain a copy of the documentation of the shortage or the specific medical need in the pharmacy records for three years from the date of receipt of the documentation.
(4) is made with any component not intended for use in a CSP for the intended patient population.
(5) Is made with a bulk drugs substance, as defined in Section 503A(b)(1)(A)(i), when there is an FDA approved sterile drug product that is available and appropriate for the intended CSP.
(6) cannot be sterilized within the licensed location~~pharmacy~~.

Commented [SA3]: FAQ

Commented [SA4]: FAQ on examples

(f) Prior to allowing any CSP to be compounded in a pharmacy, the pharmacist-in-charge shall complete a self-assessment, as required by Section 1715.

(g) In addition to section 1707.2 of the board's regulations, consultation shall be available to the patient and/or primary caregiver concerning proper use, storage, handling, and disposal of a CSP and CSP related supplies furnished by the pharmacy.

(h) Compounding with blood derived or other biological materials or blood components shall be done in compliance with Health and Safety Code section 1602.5.

(i) Storing, weighing, measuring, compounding, and/or performing other manipulation of an active pharmaceutical ingredient (API) or added substance deemed hazardous by Occupational Safety and Health (NIOSH) shall be done in compliance with USP Chapter 800, Hazardous Drugs-Handling in Healthcare Settings and any board regulations.

(j) Storing, weighing, measuring, compounding, and/or performing other manipulation of an antineoplastic under Occupational Safety and Health (NIOSH) shall be done in compliance with USP Chapter 800, Hazardous Drugs- Handling in Healthcare Settings and any board regulations.

1751.1. Compounding Definitions.

The definitions in in this section supplement the definitions provided in USP Chapter 797.

(a) "Compounding personnel" means any person involved with any procedure, activity or oversight of the compounding process.

(b) "Compounded sterile preparation (CSP)" means a preparation intended to be sterile which is

created by combining, admixing, diluting, pooling, reconstituting other than as provided in the FDA approved manufacturer package insert, repackaging, or otherwise altering a drug product or bulk drug substance.
(c) "Copy or essentially a copy" of a commercially available drug product means all preparations that are comparable in active ingredients to commercially available drug products, except that it does not include any preparations in which there has been a change, made for an identified individual patient, which produces for that patient a clinically significant difference, as determined by a prescribing practitioner, between that compounded preparation and the comparable commercially available drug product.

(d) "Diluent" means a liquid with no pharmacological activity used in reconstitution, such as sterile water for injection.

(e) "Designated compounding area or compounding area" means a restricted location with limited access designated for the preparation of CSP, where only activities and items related to compounding are present.

(f) "In process material or in process preparation or stock solution" means any material fabricated, compounded, blended, or derived by chemical reaction that is produced for, and used in, the preparation of the CSP. For purposes of this article, "in process material" shall refer to ~~the~~ all terms used in this subdivision.

(g) "Integrity" means retention of potency until the beyond use date provided on the label, when the preparation is stored and handled according to the label directions.

(h) "Potency" means an active ingredient's strength in a preparation which is within a specified range as determined in the facility's SOP.

(i) "Preparation" means a drug or nutrient compounded in a pharmacy; which may or may not be sterile.

(j) "Product" means a commercially or conventionally manufactured drug or nutrient evaluated for safety and efficacy by the FDA.

(k) "Quality" means the absence of harmful levels of contaminants, including filth, putrid, or decomposed substances, the absence of active ingredients other than those listed on the label, and the absence of inactive ingredients other than those listed on the master formulation document.

(l) "Strength" means amount of active ingredient per unit of a compounded drug preparation.

1751.2 PERSONNEL TRAINING AND, EVALUATION

The requirements of this section apply in addition to the requirements in USP Chapter 797.
(a) Training, evaluation, and requalification procedures for personal preparing, verifying, and/or

handling a CSP shall address the following topics:

(1) Quality assurance and quality control procedures,
(2) Container closure and equipment, selection,
(3) Component selection, and handling, and
(4) Sterilization techniques, when applicable

(b) The pharmacist responsible for or directly supervising, aseptic techniques or practices, shall demonstrate proficiency in the skills necessary to ensure the integrity, potency, quality, and labeled strength of a CSP.

(c) Aseptic manipulation evaluation and requalification documentation shall include the PEC's (Primary Engineering Control) unique identifier used during the evaluation. Aseptic manipulation evaluation and requalification shall be performed using same personnel, procedures, type of equipment, and materials used in compounding drug preparations.

(d) Requalification in hand hygiene, garbing and aseptic manipulation shall occur each time the quality assurance program yields an unacceptable result as defined in the Standard Operating Procedure (SOP)s that may indicate microbial contamination of CSPs. Requalification procedures shall be defined in the pharmacy's SOPs.

(e) Compounding personnel who fail any aspect of training or demonstrated competency, either initially or during requalification, shall not be involved in compounding a CSP until after successfully passing reevaluations in the deficient area(s).

(f) The pharmacy must document that any person assigned to provide training has obtained training and demonstrated competency in any subject in which the person will provide training or observe and measure competency.

1751.3 PERSONAL HYGIENE AND GARBING

The requirements of this section apply in addition to the requirements in USP Chapter 797.

(a) Compounding personnel experiencing any of the following: rashes, recent tattoos or oozing sores, conjunctivitis, active respiratory infection, or other conditions which could contaminate a CSP or the environment shall not be allowed to enter the designated compounding area(s).

(b) Prior to entry into the designated compounding area all hand, wrist, and other exposed jewelry or piercing shall be removed.

(c) Personnel protective equipment shall be donned and removed in an ante-area or immediately outside the segregated compounding area (SCA). Donning and doffing garb shall not occur in the ante-room or the SCA at the same time unless the pharmacy's SOP define specific processes that must be followed to prevent contamination.

(d) Eye glasses shall be cleaned as part of hand hygiene and garbing, the standards for which the pharmacy shall specify in its standard operating procedures (SOPs).

(e) RABS and pharmaceutical isolator sleeves and gloves shall be changed according to both the manufacturer's recommendations and the facility's SOP.

(f) Before any hand hygiene or garbing accommodation is granted pursuant to USP 797 Section 3.1, the designated person shall determine that the quality of the environment and any CSPs is not affected. Documentation of the determination shall be done prior to the accommodation being allowed.

1751.4 FACILITIES AND ENGINEERING CONTROLS

Commented [SA5]: Add in definition of PEC

The requirements of this section apply in addition to the requirements in USP Chapter 797**.**

(a) A sink used for compounding or hand hygiene shall not be part of a restroom or water closet.

(b) Reusable equipment and utensils which ~~have~~ cannot ~~not~~ be sterilized and depyrogenated, and that will come in direct contact with compounding components must be rinsed with either sterile water for injection or sterile water for irrigation, ~~, pyrogen free water~~.

Commented [SA6]: Reference applicable USP Chapters

Commented [SA7]: Develop a small exception for water produced. Will consider COA.

(c) If a segregated compounding area (SCA) is used:

(1) Except for walls, the SCA's visible perimeter shall be at least 1 meter from all sides of the PEC or in a separate room.

(2) Surfaces within the SCA shall 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.

(d) Any room, regardless of its ISO classification, with a PEC used for sterile compounding shall only be used for Category 1 preparation unless it is entered via an ante-room.

(e) (1) Designated compounding area(s) shall typically be maintained at a temperature of 20° Celsius or cooler and shall provide comfortable conditions for compounding personnel attired in the required garb.

(2) The temperature shall be monitored in each room of the designated compounding area each day that compounding is performed, either manually or by a continuous recording device.

(f) Where a pass-through is installed in a secondary engineering control, SOPs must address how both doors will not be opened at the same time. Effective ~~January 1, 2022~~[two years from the effective date of the regulation], all pass-throughs must be interlocking. ~~A pass-through used to access a negative pressure ISO 7 or better space from a non-classified space, must be a HEPA-filtered purge pass-through.~~

(g) When a RABS is used, an ingress and egress test shall be performed at each certification. If the main chamber of the RABS is opened, the manufacturer's purge time must be met before cleaning takes place. SOPs shall be developed and implemented to ensure compliance.

(h) No CSP shall be compounded if compounding personnel know, or reasonably should have known, that the compounding environment fails to meet criteria specified in USP Chapter 797, this article, and the pharmacy's written SOPs.

1751.5 CERTIFICATION AND RECERTIFICATION

The requirements of this section apply in addition to the requirements in USP Chapter 797.

(a)(1) Testing and certification of all classified areas shall be completed by a qualified technician who is familiar with certification methods and procedures outlined within the Controlled Environment Testing Association (CETA)'s Certification Guide for Sterile Compounding Facilities. Testing shall be performed in accordance with CETA Certification Guide for Sterile Compounding Facilities (CAG-003-2006-13, Revised 2015), which is hereby incorporated by reference. Certification shall demonstrate compliance with all standards in USP 797 and established by this article.

(2) CAG standard(s) used to perform ~~certify~~ certification testing in all classified areas to shall be recorded on certification report.

(b) SOPs shall specify steps to be taken if a classified area(s) fails to meet the specified ISO classification including the investigative and corrective actions, allowable activities, and retesting procedures. SOPs shall be followed.

(c) PECs must be recertified whenever the following occurs: 1. Repairs, 2. Alterations to the PEC that could affect airflow or air quality. Further, SOPs must address the conditions under which recertification must also be completed when relocating a PEC.

1751.6 MICROBIOLOGICAL AIR AND SURFACE MONITORING

The requirements of this section apply in addition to the requirements in USP Chapter 797.

(a) SOPs shall specify steps to be taken when the microbiological air and surface monitoring action levels are exceeded including the investigative and corrective actions, allowable activities, and resampling procedures.

(b) During biannual recertification, all microorganism recovered (growth) shall be identified by a qualified microbiologist, at least to the genus ~~species~~level, regardless of the cfu count. When identification of an organism of concern, action shall be taken. Organisms of concern shall be identified by the PIC or designated person and shall be documented in a SOP. Some possible

organisms of concern ~~would~~ may, but need not, include~~be~~ gram-negative rods, coagulase positive staphylococcus, and certain molds and yeasts.

(c)Whenever ~~growth is identified~~ cfu action levels are exceeded or an organism of concern is identified as specified in (a) or (b), required action shall include at a minimum, an investigation of (1) cleaning and compounding operations, (2) sampling, (3) personnel training, (4) incubator functionality, (5) facility management, and (6) resampling. Consultation with a competent microbiologist, infection control professional, or industrial hygienist is required when resampling results in growth of an organism of concern or when action levels are exceeded, regardless of count. All actions taken shall be documented.

(d) The designated person shall review the sampling results and identify data trends at least every time sample results are received. The designated person shall evaluate trends to determine if corrective action is needed. The results of the review shall be documented.

(e) Environmental sampling shall be done in compliance with CETA Certification Application Guide USP <797> Viable Environmental Sampling & Gowning Evaluation (CAG-009, current version-20XX-XX, Revised XX), which is hereby incorporated by reference.

1751.7 CLEANING, DISINFECTING, AND APPLYING SPORICIDAL AGENTS IN COMPOUNDING AREAS

The requirements of this section apply in addition to the requirements in USP Chapter 797.

(a) Cleaning, disinfection, and sporicidal agents shall be used in accordance with manufacturers' specifications.

(b) Reusable cleaning supplies shall not be stored within 1 meter of the PEC.

1751.8 INTRODUCING ITEMS INTO THE SEC AND PEC

The requirements of this section apply in addition to the requirements in USP Chapter 797**.**

(a) SOPs shall define the process and products to be used on any equipment and other items entering from an unclassified area into the clean side of the ante-room, entering a PEC, and entering the SCA. ~~This~~ These SOPs will define at a minimum, what product is to be used, the dwell time required, and how dwell time will be monitored and documented.

1751.9 EQUIPMENT, SUPPLIES, AND COMPONENTS

The requirements of this section apply in addition to the requirements in USP Chapter 797.

(a) All equipment and supplies used to compound CSP shall be used, in accordance with

manufacturers' specifications and be of suitable composition such that the surfaces which contact components are not reactive or sorptive.

(b) Incubators used by the pharmacy shall be cleaned, maintained, calibrated, and operated in accordance with manufacturers' specifications. For incubators without specific manufacturers' specifications, cleaning shall take place at least monthly and calibration shall take place at least every 12 months. SOPs shall specify the frequency and process cleaning, maintenance, and calibration, including when incubation of samples is taking place such that samples are not compromised. All cleaning, maintenance, and calibration shall be documented.

(c) Any component used to compound a CSP shall be used and stored (1) considering issued Guidance Documents and Alerts (2) in accordance with all industry standards including the following:

(~~1~~A) United States Pharmacopeia (USP) – National Formulary (NF),

(~~2~~B) Food Drug and Cosmetic Act (FD&CA) and federal regulations adopted to implement that act,

(~~3~~C) Food Drug Administration (FDA) requirements and ~~considering issued Guidance Documents and Alerts~~, and

(~~4~~D) Manufacturers' specifications and requirements.

Commented [SA8]: Should this be rephrased.

(d) Any active pharmaceutical ingredient (API) or added substance used to compound a CSP shall be obtained from an FDA-registered facility and shall be accompanied by a valid certificate of analysis (COA). This COA shall be, at minimum, in English and shall at least meet the requirements of USP Chapter 1080, - - Bulk Pharmaceutical Excipient-Certificate of Analysis. All COAs shall be readily retrievable for at least 3 years from last use in CSP.

(e) No component shall be used to compound a CSP that meets only the European Pharmacopoeia standards, Japanese Pharmacopoeia standards, dietary supplement standards (such as USP-NF dietary monographs), food ingredient standards (such as Food-Chemical Codex (FCC)), food additive standards (such as General Standard for Food Additive (GSFA)), reagent standard (such as American Chemical Society (ASC)) or is of unspecified quality.

(f) Sterilization and depyrogenation of supplies and/or container–closure systems shall be done in compliance with USP Chapter 1229, Sterilization of Compendial Articles.

1751.10 STERILIZATION AND DEPYROGENATION

The requirements of this section apply in addition to the requirements in USP Chapter 797.

(a) Dry heat depyrogenation shall be done in compliance with USP Chapter 1228.1, Dry Heat Depyrogenation.

(b) Sterilization by filtration shall be done in compliance with USP Chapter 1229.4, Sterilizing Filtration of Liquids.

(c) Sterilizing filters used must be labeled for pharmaceutical use and reflect a sterilizing grade.

(d) Steam sterilization shall be done in compliance with USP Chapter 1229.1, Steam Sterilization by Direct Contact.

(e) Dry heat sterilization shall be done in compliance with USP Chapter 1229.8, Dry Heat Sterilization.

(f) A pharmacy shall not compound a CSP from nonsterile components when the pharmacy cannot sterilize the CSP appropriately with steam sterilization, dry heat sterilization or sterilization by filtration.

1751.11 MASTER FORMULATION AND COMPOUNDING RECORDS

The requirements of this section apply in addition to the requirements in USP Chapter 797.

(a) A CSP shall not be compounded until the pharmacy has first prepared a written master formulation document in compliance with USP Chapter 797 and identified in that document the following additional elements:

(1) Active pharmaceutical ingredient (API) or added substance(s) and their amounts, which shall include, at a minimum, salt form and purity grade, when available,
(2) Container–closure systems to be used, which shall include, container and closure types and volume(s).
(3) The source referenced to assign the BUD; each source referenced shall be readily retrievable at the time of compounding and shall be maintained for three years from the date each CSP is dispensed.
(4) Instructions for storage and handling of the compounded drug preparation.

(b) Where a pharmacy does not routinely compound a particular drug preparation, the master formulation record for that preparation may be recorded on the prescription document itself. This record shall comply with USP Chapter 797 and this section.

(c) A compounding record shall be a single document. The document shall satisfy the requirements of USP Chapter 797, as well as the following:

(1) The date and time of preparation. The time of preparation is the time when compounding the CSP started, which also determines when the assigned BUD starts.
(2) The assigned internal identification number shall be unique for each compounded drug preparation.
(3) The vendor (manufacturer/repackager), lot number, and expiration date shall be recorded for each component for CSPs. Documenting solely the National Drug Code (NDC) does not meet this requirement.
(4) The total quantity compounded shall include the number of units made and either the

volume or the weight of each unit.
(5) The identity of each person performing the compounding and pharmacist verifying the final drug preparation
(6) When applicable, endotoxin level calculations and readings.

~~1735~~1751.12 RELEASE TESTING

The requirements of this section apply in addition to the requirements in USP Chapter 797.

(a) A pharmacist performing, or supervising compounding is responsible for the integrity, potency, quality, and labeled strength of a compounded drug preparation until the beyond use date indicated on the label, when label instructions for storage and handling are followed after the preparation is dispensed.

(b) Validation of an alternative method for sterility testing shall be done in compliance with USP Chapter 1223, Validation of Alternative Microbiological Methods showing it to be non-inferior to USP Chapter 71, Sterility Tests, and shall demonstrate the method to be suitable for each CSP formulation for which the alternate method is used.

(c) Except for CSPs made for inhalation or ophthalmic administration, prior to releasing a CSP made from one or more nonsterile component(s) the pharmacy shall review and document the results of bacterial endotoxin testing. Results shall be documented in the compounding record.

1751.13 LABELING

The requirements of this section apply in addition to the requirements in USP Chapter 797.

(a) A CSP label shall also include the following:
(1) For admixed CSP, the solution utilized; and
(2) Name and contact information of the compounding pharmacy and, if different, the dispensing pharmacy;
(3) Instructions for administration. For admixed CSP solutions, the rate of infusion, or range of rates in infusion, or the duration when the entire CSP is administered.

(b) Any compounded drug preparation dispensed to a patient or readied for dispensing to a patient shall also include on the label the information required by Business and Professions Code section 4076 and section 1707.5.

1751.14 ESTABLISHING BEYOND-USE DATES

The requirements of this section apply in addition to the requirements in USP Chapter 797.

(a) A CSP's beyond use date (BUD) shall not exceed:
(1) The chemical and physical stability data of the API and any added substances in the preparation,
(2) The compatibility of the container–closure system with the finished preparation (e.g., possible leaching, interactions, and storage conditions),
(3) shortest remaining expiration date or BUD of any of the starting components.

(b) A CSP labeled with a BUD with only a date shall expire at midnight at that date.

(c) Prior to the dispensing a CSP that requires sterility and pyrogen testing, the pharmacy shall receive test results and ensure that the results are within acceptable limits. The pharmacy shall retain the results as part of the compounding record.

(d) A CSP shall not be assigned a longer BUD based on an unvalidated alternative microbiological method.

1751.15. USE OF CONVENTIONALLY MANUFACTURED PRODUCTS AS COMPONENTS
The requirements of this section apply in addition to the requirements in USP Chapter 797.

If a single-dose container is entered or punctured outside of an ISO Class 5 area, the product must be discarded immediately.

1751.16. USE OF CSPS AS COMPONENTS

The requirements of this section apply in addition to the requirements in USP Chapter 797.

(a) Where an in process material is nonsterile, it shall be treated as a sterile product for purposes of this article.

1751.17 Standard Operating Procedures (SOPS)

The requirements of this section apply in addition to the requirements in USP Chapter 797.

(a) Standard operating procedures (SOPs) shall:
(1) Comply with USP Chapter 1163, Quality Assurance in Pharmaceutical Compounding,
(2) In addition to the SOP SOPs listed in USP Chapter 1163, Quality Assurance in Pharmaceutical Compounding, include:
(A) Methods by which the supervising pharmacist will the quality of compounded drug preparations.
(B) Procedures for handling, compounding and disposal of infectious materials. The written SOPs shall describe the pharmacy protocols for cleanups and spills in

conformity with local health jurisdictional standards.

(C) The methods a pharmacist will use to determine and approve the ingredients and the compounding process for each preparation before compounding begins

(b) Any pharmacy engaged in compounding CSPs shall maintain and follow written SOPs for compounding.

(c) The SOPs shall be reviewed on an annual basis by the pharmacist-in-charge. Such review shall be documented by the pharmacist-in-charge. The SOPs shall be updated whenever changes are implemented. Such changes shall be disseminated to the affected staff prior to implementation.

1751.18 QUALITY ASSURANCE AND QUALITY CONTROL

The requirements of this section apply in addition to the requirements in USP Chapter 797.

(a) The quality assurance program shall comply with section 1711 and USP Chapter 1163, Quality Assurance in Pharmaceutical Compounding. In addition, the program shall include:

(1) A written procedure for scheduled action in the event any compounded drug preparation is ever discovered to be outside expected standards for integrity, potency, quality, or labeled strength.

(2) A written procedure for responding to out-of-range temperature and humidity variations within the pharmacy and within patient care areas where a furnished drug may be returned for furnishing to another patient.

(3) A written procedure addressing each of the USP Chapter 1163's integrated components and standard operating procedures.

(4) Quality assurance program shall be compliant with section 1711.

(b) The pharmacy shall process recalls and adverse event reporting in compliance with Business and Professions Code section 4127.8.

(c) All complaints related to a potential quality problem with a compounded drug preparation and all adverse events shall be reviewed by the pharmacist-in-charge. Such review shall be documented and dated.

1751.19 CSP HANDLING, PACKAGING, STORAGE, AND TRANSPORT

The requirements of this section apply in addition to the requirements in USP Chapter 797.

(a) There shall be a defined process and documented procedure to ensure temperature sensitive products will arrive at their desired destinations after transporting within the expected quality standards for integrity, potency, quality and labeled strength.

(b) Packaging materials shall protect CSPs from damage, leakage, contamination, degradation, and adsorption while preventing inadvertent exposure to transportation personnel.

(c) A pharmacist supervising compounding is responsible for the proper preparation, labeling, storage, and delivery of the compounded drug preparation.

1751.20 DOCUMENTATION

The requirements of this section apply in addition to the requirements in USP Chapter 797.

(a) Pharmacies shall maintain each record required by USP Chapter 797 or this article in the pharmacy, in a readily retrievable form, for at least three years from the date the record was last used. If only recorded and stored electronically, on magnetic media, or in any other computerized form, the records shall be maintained as specified by Business and Professions Code section 4070.

(b) Records created shall be maintained in a manner to allow for all versions of the document to be viewed. When a change to a record must be made, the record's original text must be maintained, and the record must reflect each change, the person who made the change, and the date and time the change was made.

1751.21 COMPOUNDING ALLERGENIC EXTRACTS

The requirements of this section apply in addition to the requirements in USP Chapter 797.

(a) Any allergenic extract compounding shall take place in a dedicated PEC. No other CSP may be made in this PEC.

(b) All required documentation for a Category 1 or Category 2 CSPs are required for allergenic extract compounding. (i.e. Compounding records, labeling, cleaning, temperatures logs, patient specific prescriptions etc.)

CALIFORNIA HOSPITAL ASSOCIATION

Providing Leadership in Health Policy and Advocacy

DATE: October 17, 2019

TO: Medication Safety Committee Members

FROM: BJ Bartleson, MS, RN, NEA-BC, Vice President, Nursing & Clinical Services

SUBJECT: USP 800 Hazardous Drugs – Handling in Healthcare Settings

SUMMARY

At our last meeting, we discussed USP 800 and hospital implications. During the postponement and pending resolution of the appeals of 795, & 797, 800 is informational and not compendially applicable, however, USP encourages utilization of 800 in the interest of advancing public health. The committee also discussed Cal OSHA's outstanding interpretation and definitions of USP 800 hazardous drugs.

CHA has learned that Cal OSHA has not resumed its discussions on USP 800, and we are unaware of when that will occur. In the meantime, CHA seeks advice from members on next steps.

DISCUSSION

1. Are there standardized actions all hospitals will take or are these issues hospital specific?
2. Do the committee members think additional education, tools or action are necessary relative to USP 800?

ACTION REQESTED

- Information and advice to CHA on next steps

Attachments: USP 800 Overview Presentation

BJB:br

USP 800 Hazardous Drugs – Handling in Healthcare Settings
Official December 1, 2019

CEDARS-SINAI
LEADING THE QUEST™

cedars-sinai.edu

Agenda

1. Definitions
2. Scope
3. CSMC Multidisciplinary Task Force
4. Key Requirements and Operational Impacts
5. Hazardous Communication Plan and Training
6. Personnel Protective Equipment
7. Medical Surveillance
8. Workforce Considerations
9. FY 20 Budget Impact

2

What is USP 800 Hazardous Drugs

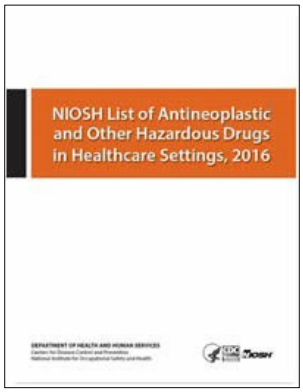
- Based on published reports of adverse effects in healthcare personnel from occupational exposure to HDs
- USP 800 consistent of 18 chapters (see Appendix)
- Any drug defined as hazardous by the National Institute for Occupational Safety and Health (NIOSH) on the basis of at least one of six criteria:
  1. Carcinogenicity
  2. Teratogenicity or developmental toxicity
  3. Reproductive toxicity in humans
  4. Organ toxicity at low doses in humans or animals
  5. Genotoxicity
  6. New drugs that mimic existing hazardous drugs in structure or toxicity

National Institute for Occupational Safety and Health (NIOSH)

Categories

1. Antineoplastics (e.g.,chemotherapy)
2. Non-antineoplastics that meet 1 or more criteria and may pose reproductive risk for some populations
3. Reproductive only hazards
4. Investigational drugs-if no information available

HDs are ubiquitously used throughout the medical center and include, infusions, injections, ophthalmic, inhalation, oral and topic drugs

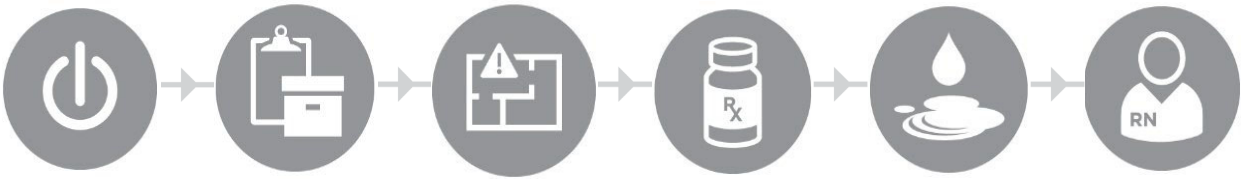


https://www.cdc.gov/niosh/docs/2016-161/images/2016-161.jpg, accessed 9/30/18

USP 800
Hazardous Drugs (HDs)

- Designed to protect employees, patients and the general public who may be accessing facilities where hazardous drugs (HDs) are stored, prepared, transported or administered.
- Includes but not limited to
  - Pharmacists, technicians, nurses, physicians, respiratory therapists, environmental services staff, allied health professionals, other healthcare workers, patients, families
- Applies to entities that handle HDs
  - Pharmacies, hospitals and other healthcare institutions, clinics, physicians' offices or veterinarians' offices
- **Employees <u>must</u> receive HD training and be assessed for an understanding of the training**.

Hazardous Drug Lifecycle



Getting Started – People and Processes

Receiving and Storage

Infrastructure for Compounding

Compounding HD and the Necessary PPE

Spills, Cleaning and Disposal

Administering HDs and the Necessary PPE

6

USP 800 Key Components
(see Appendix for complete list)

- Hazardous Drug (HD) List Risk Assessment
- Hazardous Drug Communication Plan and Training
- Operations
  - Hospital flow of HDs
  - Personnel Protective Equipment
  - Containment of HDs
    - Ex: If non-antineoplastic or reproductive risk HD drugs require crushing tablet(s) or opening capsule(s), containment and work practices defined in the risk assessment must be used (e.g. appropriate personnel protective equipment (PPE), plastic pouch to contain any dust or particles generated).
  - Cleaning of medication rooms, patient rooms
  - Waste management including storage
  - Job descriptions and Job Hazard Analysis-incorporate HD handling
- Monitoring
  - Employees-Medical Surveillance
  - Facilities

7

CSMC USP 800 Hazardous Drug Task Force

- Established multidisciplinary team in 2017
- Goal: Develop policies, standard operating procedures and conduct risk assessment to Hazardous Drugs List to support education, training and management of HDS

1. Nursing
2. Pharmacy
3. ORs
4. Epidemiology
5. Infusion Centers
6. Ambulatory Clinics
7. Human Resources
8. OLAR
9. Respiratory Therapy
10. Purchasing
9. EVS
10. Environmental Safety
11. Physicians
12. Employee Health
13. Transporters
14. Facility Services
15. Supply Chain
16. EIS
17. SOCCI, THO, TACRI and Valley Oncology Group
18. MDR

8

Hazard Communication Program Plan

- 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 Safety Data Sheet (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. Chapter applies to anyone capable of reproduction.

http://www.usp.org/sites/default/files/usp/document/our-work/healthcare-quality-safety/general-chapter-800.pdf, accessed 13119
http://www.usp.org/frequently-asked-questions/hazardous-drugs-handling-healthcare-settings, accessed 13119

9

Workforce Considerations: USP 800 Scenario

Organizations should establish a mechanism by which those workers who are actively trying to conceive, are pregnant, or are breast-feeding can request alternative duty or protective reassignment.
https://www.osha.gov/SLTC/hazardousdrugs/controlling_occex_hazardousdrugs.html, accessed 13119

- Scenario: Healthcare worker notifies Cedars that they want to start a family and are starting IVF and then intends to breastfeed for 12 months. Where will the worker be assigned? For how long? Should others pick up the employee's workload? Should there be a cross-trained workforce to cover shifts?

10

USP <800> Hazard Communication Program at Other Hospitals- 01/16/2019

Hospital	How are you identifying applicable employee types?	How are you identifying applicable employees?	At what point within the employment process are you notifying employees, and what tools are you using?
Penn Medicine	All employees	All employees	1. Outlined in job description, which is signed upon hire. 2. Annual performance evaluation, additional USP 800 document
Nebraska Medicine	All employees	All individuals with applicable job titles/roles	Upon hire Tools: Internal learning/training management software system AND simple paper forms that get filed
Ochsner Health System	All employees **Rationale:** Any employee may walk through a facility and have the potential for exposure to hazardous drug residue on surfaces.	**Training for Jobs with Hazardous Drug Handling duties/Direct Patient Care** Specific online training upon hire and annually • More detailed attestation of awareness of risk • Training and attestation speak to the risk for all people of child bearing years • Understanding of steps to protect themselves and others • Agreement to follow policies and procedures	**All Employees** "USP 800 Awareness " online training module upon hire and annually. Time" five minutes • Reproductive risk is addressed but not in detail • Attestation of awareness of risk, training and understanding of steps to protect themselves and others • Agreement to follow policies and procedures. • Recognition of the HD symbol.
University of Wisconsin Health	Those who might enter a patient care area	All individuals with applicable job titles/roles	1. Upon hire - added to onboarding checklists for RNs, hazardous drug training for RNs 2. Annual education renewal - included in annual safety and infection control Tools: Internal learning/training management software

11

Personnel Protective Equipment Requirements
Will be embedded at the drug level in CS-Link for all HDs identified in risk assessment

CSMC Recommended Minimum Standards for Personal Protective Equipment for Hazardous Drug Administration

HD 1: Antineoplastic

Double chemotherapy gloves
Gown (for injectable medications)
Face shield and goggles if liquid could splash

HD 2: Non-Antineoplastic Hazardous

Formulation/Scenario	Activity	Gloving Requirements	Gowning Requirements	Eye/Face Requirements	Respiratory Requirements
Intact tablet or capsule	Administration from unit-dose package	Single chemo gloves	No gown	None	None
Manipulating tablets or capsules	Crushing tablets or capsules; handling uncoated or cut tablets for administration	Double chemo gloves	No gown	None	Mask
Oral liquid drug or feeding tube	Administration	Double chemo gloves	Gown	Face shield and goggles, if vomit or potential to spit up	None
Topical drug	Administration	Double chemo gloves	No gown	Face shield and goggles, if liquid that could splash	None
Injectable	Preparation (withdrawing from vial/mixing)	Double chemo gloves	Gown	Face shield and goggles, if liquid that could splash	None
	Administration from prepared syringe or IV bag	Double chemo gloves	Gown	None	None
Solution for irrigation	Administration (bladder, HIPEC, limb perfusion, etc.)	Double chemo gloves	Gown	Face shield and goggles, if liquid that could splash	None
Powder/solution for inhalation/serosol treatment	Administration	Double chemo gloves	Gown	Face shield and goggles, if liquid that could splash	Mask
Any hazardous medication	If patient could vomit or spit up	Double chemo gloves	Gown	Face shield and goggles, if liquid that could splash	None
Any hazardous medication	If liquid could splash	Double chemo gloves	Gown	Face shield and goggles, if liquid that could splash	None

HD 3: Reproductive Risk- PPE ABOVE ONLY REQUIRED FOR AT-RISK PERSONNEL
(Personnel who are pregnant, possibly pregnant or trying to conceive (male or female))

Additional PPE may be added in any situation with a higher risk of exposure
Adapted from NIOSH 2016 Table 5

12

Recommended Medical Surveillance Content for HD Handlers

CSMC Surveillance Plan
To be determined in collaboration with:
Peggy Miles, MD,
Jonathan Grein, MD,
Sarah Kilpatrick, MD,
Risk Management,
HR,
Employee Health

	NIOSH (1)	(2)	ONS (3)	ISOPP (4)	ashp (5)	OSHA (6)	USP (7)
Medical and exposure history	✓	✓	✓	✓	✓	✓	✓
Physical exam	✓	✓	✓	✓	✓	✓	✓
Routine labs	✓	✓	✓	✓	✓	✓	✓
Specialized tests	✓ *		✓ *	✓ **		✓ ***	✓ ***

* Biological monitoring as needed for workers who have shown health changes suggesting toxicity or who have experienced acute exposure (spill)
** Follow up recommended for workers who have shown health changes and/or have been exposed to HDs.
*** Post-exposure evaluation is tailored to the type of exposure; treatment and laboratory studies follow as indicated

1. NIOSH [2013]. Medical Surveillance for Healthcare Workers Exposed to Hazardous Drugs. National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2013-103. [http://www.cdc.gov/niosh/docs/wp-solutions/2013-103/pdfs/2013-103.pdf]. NIOSH [2004]. NIOSH alert: preventing occupational exposure to antineoplastic and other hazardous drugs in health care settings. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2004-165.
2. Department of the Army (2014). Technical Bulletin. Occupational and Environmental Health. Occupational Health and Industrial Hygiene Guidance for the Management, use and Disposal of Hazardous Drugs.
3. Polovich, M [2011]. Safe handling of hazardous drugs. 2nd ed. Pittsburgh, PA: Onc Nurs Soc.
4. ISOPP (International Society of Oncology Pharmacy Practitioners) [2007]. Standards of Practice. Safe Handling of Cytotoxics.
5. ASHP (American Society of Health-System Pharmacists) [2006]. Guidelines on handling hazardous drugs. Am J of Health Syst Pharm 63:1172-1193.
6. OSHA [1999]. OSHA technical manual, TED 1-0.15A, Sec VI, Chapt II: Categorization of drugs as hazardous. [www.osha.gov/dts/osta/ otm/otm_vi/otm_vi_2.html#2]. Date accessed:

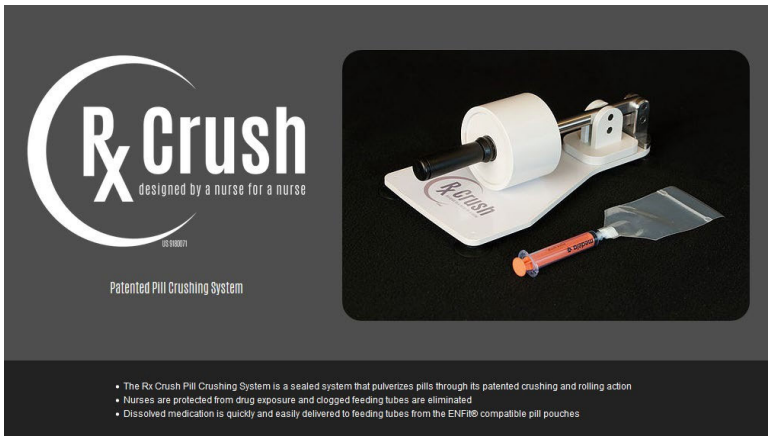
13

USP 800 Hazardous Drugs – Chapter and Status

1. List of HD (90% done)
2. Type of Exposure (done)
3. Responsibilities Personnel Handling HD (70% done)
4. Facilities & Engineering Controls (80% done, contingent on Facility completion)
5. Environmental Quality and Control (not started; Wipe Sampling)
6. Personal Protective Equipment (90% done)
7. HD Communication Program (50% done)
8. Personnel Training (to start 8/19)
9. Receiving (9/17 done)
10. Labeling (1/19 done), Packaging, Transport, Disposal (9/17 done)
11. Dispensing Final Dosage Forms (80% done)
12. Compounding (90% done)
13. Administering (90% done)
14. Deactivating, Decontaminating, Cleaning, Disinfecting (80% done)
15. Spill Control (80% done)
16. Documentation & SOPs (50% done)
17. Medical Surveillance (50% done)

14

Pill Crushing System – Self Contained; Works with ENFit*



*ENfit™ Prevention of enteral feeding misconnection, required in California, effective 7/16. Manufacturer issues delayed implementation

- Self-contained
- Current disposable device: $4.35/dose
- Rx Crush Cost:
  Device: $225-does not come into contact with medication
  Bag: $1.00/dose

15 https://www.bing.com/videos/search?q=rxcrush&pc=MOZI&ru=%2fsearch%3fq%3drxcrush%26pc%3dMOZI%26form%3dMOZLBR&view=detail&mmscn=vwrc&mid=50C65E2E547C23B1499950C65E2E547C23B14999&FORM=WRVORC, accessed 13119

Key Considerations

–Hazard Communication Plan and Workforce Considerations
- Determination of employee job classifications to be training
- Contingency planning for staffing based on reproductive concerns

–Budget impact of Personnel Protective Equipment and disposables across CSHS

–Medical Surveillance scope decision

–Waste management and storage

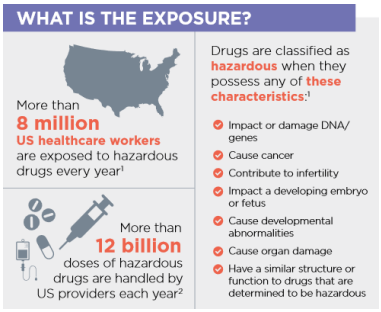
–CSHS unlicensed sites compliance determination

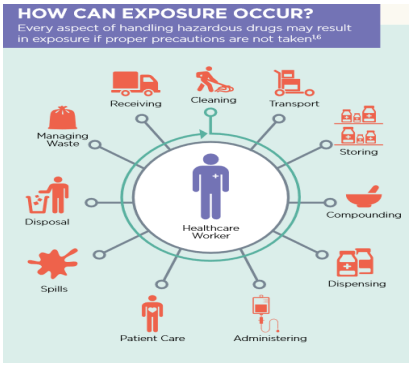
16

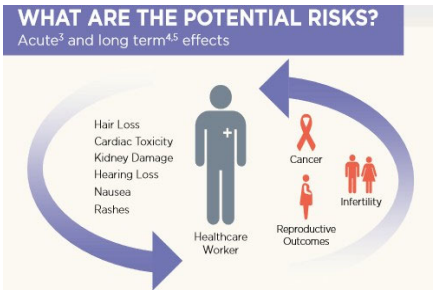
Appendix

17

USP 800 Infographic (excerpt)







http://www.usp.org/compounding/general-chapter-hazardous-drugs-handling-healthcare, accessed 13119

USP 800 Hazardous Drugs Chapters

1. Introduction Scope
2. List of HD
3. Type of Exposure
4. Responsibilities of Personnel Handling HDs
5. Facilities & Engineering Controls
6. Personnel Training
7. Personal Protective Equipment
8. HD Communication Program
9. Personnel Training
10. Receiving
11. Labeling, Packaging, Transport, Disposal
12. Dispensing Final Dosage Forms
13. Compounding
14. Administering
15. Deactivating, Decontaminating, Cleaning, Disinfecting
16. Spill Control
17. Documentation & SOPs
18. Medical Surveillance

19

PPE Unit Costs – Pharmacy Sterile Compounding Areas Estimate

PPE Item	Cost Per Unit	Est Pharmacy Cost/Day
Gloves: Sterile chemo	$1.35	x 300 = $405
Mask (isolation)	$0.05	x 200 = $10
Mask surgical duckbill	$0.08	x 50 = $4
Mask N95	$1.14	x 50 = $57
R95 Mask (Odors cleaning soln)	$3.19	
Bouf Surg Cap	$0.03	x 300 = $9
Isolation gown (yellow)	$0.52	N/A
Chemo gown	$0.83	x 75 = $63
Splashguard Visor Mask (Can be Reusable)	$0.46	N/A
Eye shield (Can be Reusable)	$1.21	N/A
Goggles (Can be Reusable)	$0.23	N/A
Chemo Spill Kit	$24.35	Rarely used
PAPR	Reusable – cleaning required-Cartridges costs	
Closed System Transfer Devices	Varied	12 month Expense in Pharmacy $400,000

Need estimated costs for additional areas(non-sterile compounding, pharmacy, nursing, EVS, dietary, etc)

CALIFORNIA HOSPITAL ASSOCIATION

Providing Leadership in Health Policy and Advocacy

DATE: October 17, 2019

TO: Medication Safety Committee Members

FROM: Candace Fong, Pharm D., System Director, Pharmacy and Medication Safety, Dignity Health

SUBJECT: Inventory Reconciliation from Automatic Dispensing Units

SUMMARY

There continues to be lack of clarity over automated dispensing units (ADUs) and inventory reconciliation of them in hospitals. The Board of Pharmacy Enforcement Committee has been discussing, and Candace attended the last committee meeting and testified. Ms. Fong informed us at the last CHA Medication Safety Committee meeting that Board of Pharmacy Legal staff will be evaluating the definition of "satellite" to determine if it includes ADUs.

DISCUSSION

1. Are hospital members clear on the different names and types of narcotic cabinets and how they need to be reconciled?
2. Does CHA need to develop policy for changes in this area?
3. What are the narcotic cabinet requirements for licensure?
4. Do we need to develop educational tools to inform hospitals?

ACTION REQESTED

- Information and advice to CHA on next steps

Attachments: 1715.65. Inventory Reconciliation Report of Controlled Substances
Inventory Reconciliation Regulation – Summary and FAQs

BJB:br

Title 16. Board of Pharmacy
Order of Adoption

Adopt section 1715.65 in Article 2 of Division 17 of Title 16 of the California Code of Regulations to read as follows:

1715.65. Inventory Reconciliation Report of Controlled Substances

(a) Every pharmacy, and every clinic licensed under sections 4180 or 4190 of the Business and Professions Code, shall perform periodic inventory and inventory reconciliation functions to detect and prevent the loss of controlled substances.

(b) The pharmacist-in-charge of a pharmacy or consultant pharmacist for a clinic shall review all inventory and inventory reconciliation reports taken, and establish and maintain secure methods to prevent losses of controlled drugs. Written policies and procedures shall be developed for performing the inventory reconciliation reports required by this section.

(c) A pharmacy or clinic shall compile an inventory reconciliation report of all federal Schedule II controlled substances at least every three months. This compilation shall require:
   (1) A physical count, not an estimate, of all quantities of federal Schedule II controlled substances. The biennial inventory of controlled substances required by federal law may serve as one of the mandated inventories under this section in the year where the federal biennial inventory is performed, provided the biennial inventory was taken no more than three months from the last inventory required by this section;
   (2) A review of all acquisitions and dispositions of federal Schedule II controlled substances since the last inventory reconciliation report;
   (3) A comparison of (1) and (2) to determine if there are any variances;
   (4) All records used to compile each inventory reconciliation report shall be maintained in the pharmacy or clinic for at least three years in a readily retrievable form; and
   (5) Possible causes of overages shall be identified in writing and incorporated into the inventory reconciliation report.

(d) A pharmacy or clinic shall report in writing identified losses and known causes to the board within 30 days of discovery unless the cause of the loss is theft, diversion, or self-use in which case the report shall be made within 14 days of discovery. If the pharmacy or clinic is unable to identify the cause of the loss, further investigation shall be undertaken to identify the cause and actions necessary to prevent additional losses of controlled substances.

(e) The inventory reconciliation report shall be dated and signed by the individual(s) performing the inventory, and countersigned by the pharmacist-in-charge or professional director (if a clinic) and be readily retrievable in the pharmacy or clinic for three years. A countersignature is not required if the pharmacist-in-charge or professional director personally completed the inventory reconciliation report.

(f) A new pharmacist-in-charge of a pharmacy shall complete an inventory reconciliation report as identified in subdivision (c) within 30 days of becoming pharmacist-in-charge. Whenever possible an outgoing pharmacist-in-charge should also complete an inventory reconciliation report as required in subdivision (c).

(g) For inpatient hospital pharmacies, a separate quarterly inventory reconciliation report shall be required for federal Schedule II controlled substances stored within the pharmacy and for each pharmacy satellite location.

(h) The pharmacist-in-charge of an inpatient hospital pharmacy or of a pharmacy servicing onsite or offsite automated drug delivery systems shall ensure that:

(1) All controlled substances added to an automated drug delivery system are accounted for;

(2) Access to automated drug delivery systems is limited to authorized facility personnel;

(3) An ongoing evaluation of discrepancies or unusual access associated with controlled substances is performed; and

(4) Confirmed losses of controlled substances are reported to the board.

Authority cited: Section 4005, Business and Professions Code. Reference: Sections 4008, 4037, 4080, 4081, 4101, 4104, 4105, 4105.5, 4110, 4113, 4119.1, 4180, 4181, 4182, 4186, 4190, 4191, 4192, and 4332, Business and Professions Code and 1261.6, Health and Safety Code.

Inventory Reconciliation Regulation – Summary and FAQs

California Code of Regulations, title 16, section 1715.65, Inventory Reconciliation Report of Controlled Substances took effect April 1, 2018.

Each subsection of CCR section 1716.65 is summarized in the table printed here. Below the table are answers to frequently asked questions (FAQs) about the regulation.

Section 1715.65. Inventory Reconciliation Report of Controlled Substances

(a) Every pharmacy, and every clinic licensed under sections 4180 or 4190 of the Business and Professions Code, shall perform periodic inventory and inventory reconciliation functions to detect and prevent the loss of controlled substances.	Subsection (a) requires all pharmacies, and all clinics licensed under Business and Professions Code section 4180 or 4190 ("clinics"), to perform periodic inventory and reconciliation functions for all controlled drugs. (Note: No frequency of these duties is specified in the regulation except for Schedule II drugs, which are discussed below.)
(b) The pharmacist-in-charge of a pharmacy or consultant pharmacist for a clinic shall review all inventory and inventory reconciliation reports taken, and establish and maintain secure methods to prevent losses of controlled drugs. Written policies and procedures shall be developed for performing the inventory reconciliation reports required by this section.	Subsection (b) requires the pharmacist-in-charge (PIC) or the clinic's consultant pharmacist to: (1) Establish and maintain secure methods to prevent losses of controlled drugs. (2) Establish written policies and procedures for performing reconciliation reports. (3) Review all inventory and reconciliation reports.
(c) A pharmacy or clinic shall compile an inventory reconciliation report of all federal Schedule II controlled substances at least every three months. This compilation shall require: *(1) A physical count, not an estimate, of all quantities of federal Schedule II controlled substances. The biennial inventory of controlled substances required by federal law may serve as one of the mandated inventories under this section in the year*	Subsection (c) requires each pharmacy or clinic to prepare at least a **quarterly** inventory reconciliation report of all federal Schedule II medications, which is based on: (1) A physical count of all federal Schedule II medications at the time of each inventory. (2) A review of all acquisition and disposition records since the last inventory.

where the federal biennial inventory is performed, provided the biennial inventory was taken no more than three months from the last inventory required by this section; *(2) A review of all acquisitions and dispositions of federal Schedule II controlled substances since the last inventory reconciliation report;* *(3) A comparison of (1) and (2) to determine if there are any variances;* *(4) All records used to compile each inventory reconciliation report shall be maintained in the pharmacy or clinic for at least three years in a readily retrievable form; and* *(5) Possible causes of overages shall be identified in writing and incorporated into the inventory reconciliation report.*	(3) A comparison of 1 and 2 to identify any differences (losses or overages). Collection and retention of records to compile each inventory report. The report must identify the possible causes of overages.
(d) A pharmacy or clinic shall report in writing identified losses and known causes to the board within 30 days of discovery unless the cause of the loss is theft, diversion, or self-use in which case the report shall be made within 14 days of discovery. If the pharmacy or clinic is unable to identify the cause of the loss, further investigation shall be undertaken to identify the cause and actions necessary to prevent additional losses of controlled substances.	Subsection (d) requires a pharmacy or clinic to file a report of losses and known causes to the board within 30 days of discovery or within 14 days if theft, self-use or diversion by a board licensee is the cause. If the cause is unknown, this section requires the pharmacy or clinic to further investigate to identify the causes and to take corrective action to prevent additional losses.
(e) The inventory reconciliation report shall be dated and signed by the individual(s) performing the inventory, and countersigned by the pharmacist-in-charge or professional director (if a clinic) and be readily retrievable in the pharmacy or clinic for three years. A countersignature is not required if the pharmacist-in-charge or professional director personally completed the inventory reconciliation report.	Subsection (e) requires the inventory reconciliation report to be signed and dated by the individual(s) performing the inventory and countersigned by the PIC or professional director (for a clinic).

(f) A new pharmacist-in-charge of a pharmacy shall complete an inventory reconciliation report as identified in subdivision (c) within 30 days of becoming pharmacist-in-charge. Whenever possible an outgoing pharmacist-in-charge should also complete an inventory reconciliation report as required in subdivision (c).	Subsection (f) requires a new PIC to complete an inventory reconciliation report within 30 days of becoming PIC. Encourages the outgoing PIC to do a reconciliation report before leaving.
(g) For inpatient hospital pharmacies, a separate quarterly inventory reconciliation report shall be required for federal Schedule II controlled substances stored within the pharmacy and for each pharmacy satellite location.	Subsection (g) requires INPATIENT HOSPITAL PHARMACIES to complete a separate quarterly inventory reconciliation report for federal Schedule II drugs stored within the pharmacy and for each of the pharmacy's satellite locations.
(h) The pharmacist-in-charge of an inpatient hospital pharmacy or of a pharmacy servicing onsite or offsite automated drug delivery systems shall ensure that: *(1) All controlled substances added to an automated drug delivery system are accounted for;* *(2) Access to automated drug delivery systems is limited to authorized facility personnel;* *(3) An ongoing evaluation of discrepancies or unusual access associated with controlled substances is performed; and* *(4) Confirmed losses of controlled substances are reported to the board.*	Subsection (h) requires the PIC of any pharmacy servicing an AUTOMATED DRUG DELIVERY SYSTEM (regardless of location) to: (1) Ensure that all controlled substances added to any automated drug delivery system are accounted for. (2) Ensure that access to any automated drug delivery system is limited to authorized facility personnel only. (3) Ensure that any discrepancy or unusual access to the controlled substances in the automated drug delivery system is evaluated. (4) Ensure that confirmed losses are reported to the board timely.

FAQs about CCR section 1716.65

1. The regulation took effect April 1, 2018. Should I have performed my initial inventory beginning April 1, 2018?

No. The board expects pharmacies and clinics to transition to satisfy the inventory reconciliation requirements over a short period of time, but not necessarily by April 1. An initial physical count of the Schedule II medications is the first step.

2. Are there any drugs in addition to federal Schedule II controlled substances affected by the requirement to do a physical count and reconciliation each quarter?

No. The regulation requires a quarterly count and reconciliation of only federal Schedule II drugs. California and the federal government have separate controlled substances schedules, although there is much similarity between the two. Nevertheless, the board determined that the federal Schedule II drug list is more current and complete, and the federal list is the reference for reporting dispensing into the Controlled Substances Utilization Review and Evaluation System (CURES) in California. A pharmacy may on its own add additional drugs to its reconciliation program.

3. Can a pharmacy or clinic estimate (instead of physically counting) federal Schedule II medications for the quarterly inventory?

No. A physical count of every Schedule II medication is required for the quarterly inventory reconciliation report.

4. Subsection (a) of the regulation requires a pharmacy or clinic to "periodically" perform inventory and reconciliation functions for controlled substances. Does this mean every quarter I must count and reconcile all controlled substances?

No. However, periodically (and under federal law at least every two years) all controlled substances must be inventoried. The board encourages more frequent counting of controlled medications to identify and prevent losses of Schedule III, IV and V drugs. The regulation only specifies the frequency of reconciliation duties for federal Schedule II drugs; the appropriate frequency for all other controlled drugs should be determined by the standard of practice in the community under the circumstances of the pharmacy.

5. Does a perpetual inventory system satisfy the requirements of this regulation?

No. The use of a perpetual inventory system does not satisfy the regulation. The regulation requires both a physical count and reconciliation with all acquisitions and dispositions be performed every 90 days.

6. If I use a perpetual inventory, can I use the physical counts made for the perpetual inventory instead of physically counting the drugs specifically for the inventory reconciliation report?

It depends. The regulation requires a physical count of each Schedule II medication every quarter, which is then used as part of the inventory reconciliation analysis and report. If, for example, the pharmacy or clinic physically counts the specific drug stock each time a Schedule II drug is dispensed or acquired, that count might be used to fulfill the physical count required by the inventory reconciliation regulation, but the PIC or consultant will need additional data. For any drug where there were no dispositions or acquisitions during the quarterly reconciliation period (and therefore no physical count through the perpetual inventory system), a physical

count of the Schedule II drug must be made because each drug must be physically counted at least quarterly.

7. I have a recent physical count for each Schedule II drug. What do I compare that to? What do I do with that information?

For each medication, the PIC or consultant would start with the physical count of the medication from the last inventory reconciliation report and:

1. Add all acquisitions and subtract all dispositions that occurred during the reconciliation period (no greater than 90 days) to identify the amount of drug stock that should be on hand (expected drug stock).
2. Compare the expected drug stock to the actual physical inventory count.
3. If there is a difference, attempt to identify the source of overage or shortage. **NOTE:** If there is a discrepancy and the recent physical count is from a perpetual inventory system, the board urges the facility to initiate a supplementary physical count of the medication. Determine if the facility needs to take corrective action, including modify its policies and procedures, conduct an investigation, institute additional security or modify its practices.
4. Whether or not there is a discrepancy, the results must be recorded in your inventory reconciliation report.

8. Does an inpatient hospital pharmacy or a pharmacy servicing onsite or offsite emergency kits (e-kits) have to complete an inventory reconciliation report for the Schedule II controlled substances contained within the e-kits?

There is no specific reconciliation report for the kits themselves, although a pharmacy's replenishment of Schedule II drugs removed from the emergency kits would be part of a pharmacy's disposition of medication.

9. An inventory reconciliation report of all Schedule II drugs shall be compiled at least every three months and, in order to complete the report, the inventory must be compared with a review of drugs that entered and left the pharmacy since the previous inventory reconciliation. Since no reconciliation report exists before April 1, 2018, does that mean that the first inventory reconciliation report will not be due before July 1, 2018?

To initiate the reconciliation process and establish a baseline for future inventory reconciliation reports, a physical count of all Schedule II medications must be undertaken. The board would generally expect a pharmacy to perform this count on or after April 1, 2018. To allow time to develop meaningful written policies and procedures for the inventory reconciliation process, the board recommends a pharmacy or clinic perform the inventory counts within the first 90 days after April 1 (i.e., July 1, 2018).

Additionally, any new PIC on or after April 1, 2018, is required to prepare a report upon assuming the PIC position. Within the first three months after April 1, 2018, the board would

expect the new PIC, within 30 days, to have performed an inventory count of all Schedule II medications consistent with the requirements to prepare an inventory reconciliation report.

10. An initial inventory does not appear to be required as part of this rule change. Since a reconciliation report cannot be compiled without an initial reference count, would it be appropriate for pharmacies or clinics to perform a physical count of all Schedule II drugs during the initial three-month period (after April 1), and then begin reconciliation processes after July 1st?

Yes. See the response to question 9.

11. A PIC must complete an inventory reconciliation report within 30 days of becoming pharmacist-in-charge. If there is a PIC change on April 1, 2018, how can the PIC create a reconciliation report, given there may not be a recent inventory or reconciliation report to refer to?

In this specific case, if prior data were unavailable because of the implementation date of the regulation, the board would expect the PIC to at least perform an inventory of all Schedule II medications consistent with the requirements to prepare the reconciliation report within 30 days (May 1, 2018).

12. Should the inventory reconciliation report encompass only significant losses, as defined by the DEA, or should the report encompass any discrepancy? If the former, doesn't a pharmacy's or clinic's filing of DEA Form 106 with the DEA already provide the requested information to the board if the board receives a copy of that report?

California law requires that any loss of controlled substances be reported to the board within 30 days – and reported within 14 days where drug theft, self-use or diversion have been committed by a board licensee. These are existing requirements, predating the inventory reconciliation requirements. The reconciliation regulation restates the reporting of drug loss requirements for clarity. A DEA Form 106 may be used to make this report to the board. Also, a separate report is required to the DEA (on a Form 106) of any significant loss of a controlled substance.

13. Will the board create a new process for reporting Schedule II controlled substances drug losses? Is there a standard form or email address to submit this information?

The board will not create a new or additional process for reporting the loss of controlled substances. A DEA Form 106 or a written statement containing specified details of the loss is sufficient. Check the board's website on how to report a drug theft or loss.

14. If my pharmacy or clinic is unable to identify the cause of the loss, should we wait to report the loss to the board until the cause is determined?

No. Reporting is required for any loss of controlled substances within, at most, 30 days regardless if a cause of the loss was identified. Should a cause be identified later, an additional

report can be made to the board. If the cause is theft, diversion or self-use by a board licensee, the report must be made within 14 days.

However, the regulation also directs that "further investigation shall be undertaken to identify the cause and actions necessary to prevent additional losses of controlled substance" where the source of a loss cannot be readily identified.

15. Does a pharmacy have to maintain actual paper documents of the records used to compile each inventory reconciliation report? Are electronic records acceptable?

All records used to compile each inventory reconciliation report shall be maintained in the pharmacy or clinic for at least three years in a readily retrievable form. Provided the records are readily retrievable, electronic records are acceptable.

16. Can the inventory reconciliation report be completed by multiple persons?

Yes. All persons involved in performing the inventory must sign and date the report, which also must be countersigned by the PIC or professional director (if a clinic).

17. How do I physically count liquid Schedule II medications for the reconciliation report?

The board does not expect a count or measurement of every liquid you have as part of the quarterly reconciliation. Instead, the board recommends:

- **Where there is a unit of use container,** a pharmacist should accept the measurement printed on the container and include it in the physical count. However, if the unit of use container looks damaged or altered in some manner, treat the item as quarantined.
- **Where multidose containers are used,** a pharmacist should subtract the amount dispensed from the measurement printed on the container. Subsequently, the pharmacist should document the remaining amount on the container itself. Example: A pharmacist dispensed 240ml from a 473ml stock bottle. The pharmacist would subtract 240ml from 473ml and document the difference of 233ml on the stock bottle. The remaining amount of 233ml would be used as the physical count for the reconciliation report.

18. Can unlicensed personnel (e.g., clerks) perform the inventory necessary to complete the inventory reconciliation report?

As identified in CCR section 1793.2, the counting of pharmaceuticals is considered a "nondiscretionary task" – a duty a pharmacy technician may perform. Accordingly, unlicensed personnel cannot complete the inventory function.

19. How does a reconciliation report help detect drug diversion?

A reconciliation report aids in the identification of controlled substance inventory discrepancies. Pharmacies can respond to inventory shortages or overages by initiating a close

review, which may aid in detection of drug diversion. Recording of an inventory alone lacks review and analysis of acquisition and disposition information.

20. Wouldn't a perpetual inventory identify diversion?

A perpetual inventory is a beneficial tool and may aid in identification of drug diversion. However, a perpetual inventory with no discrepancies is not evidence of a lack of diversion. A perpetual inventory may only account for known drug acquisitions and dispositions. If acquisition invoices are destroyed or fraudulent prescriptions are processed and later deleted, a perpetual inventory may show no discrepancies. Further, all categories of drug acquisition and disposition may not be entered into a perpetual inventory.

21. The computer already counts acquisitions and dispositions of Schedule II controlled substances for the perpetual inventory. Is the count in the computer sufficient for the reconciliation report?

No. Electronic records can be used to aid in calculation of total acquisition and disposition information for the reconciliation report, but this information must be used in conjunction with an initial physical count and a final physical count to complete the requirement of CCR 1715.65. Any electronic records used should be reviewed for unauthorized manipulation and evaluated against other available records for consistency. Other records may include hard copy drug acquisition invoices, purchase orders, signatures for dangerous drug deliveries, drug acquisition summaries from wholesalers, reverse distribution documents, return to wholesaler for credit documents, drug destruction documents and/or hard copy prescription documents.

22. In an inpatient pharmacy, would "disposition" of Schedule II drugs refer to drugs that are 1) supplied into an ADDS (Pyxis, Omnicell, etc.) or as floor stock; or 2) dispensed to the patient?

In an inpatient pharmacy, disposition would refer to medications dispensed directly to the patient. Please see additional requirements for inpatient hospital pharmacies found in 1715.65(g)-(h).

23. Does the regulation require a reconciliation of <u>all</u> controlled substances or only Schedule II controlled substances?

As referenced in 1715.65(c), the compilation of a <u>quarterly</u> inventory reconciliation report is required only for all federal Schedule II controlled substances**.** However, as referenced in 1715.65(a), every pharmacy, and every clinic licensed under sections 4180 or 4190 of the Business and Professions Code, still must perform periodic inventory and inventory reconciliation functions to detect and prevent the loss of controlled substances. Additionally, other sections of pharmacy law (BPC 4081 and CCR 1718) require a pharmacy to have complete accountability of all dangerous drugs handled by every licensee.

24. Could you provide more guidance on periodic reconciliations of Schedule III – V drugs? For example, can Schedule III-V counts be estimates – as allowed for biennial inventories – or must they also be exact counts? Should Schedule III-V reconciliations be done more frequently?

CCR 1715.65(c)(1) requires a physical count, not an estimate of, of all quantities of federal Schedule II controlled substances. The regulation is silent regarding estimation of Schedule III – V counts; however, because BPC 4081 and CCR 1718 require licensees, including a pharmacy, to have complete accountability of all dangerous drugs, it is recommended Schedule III – V drugs be exact counts.

25. Subsection (a) of the regulation requires a pharmacy or clinic to "periodically" perform inventory and reconciliation functions for controlled substances. Does this mean every quarter I must count and reconcile all controlled substances?

No. However, periodically (and under federal law at least every two years) all controlled substances must be inventoried. The board encourages more frequent counting of controlled medications to identify and prevent losses of Schedule III, IV and V drugs. But the regulation only specifies the 90-day frequency of reconciliation duties for federal Schedule II drugs; the appropriate frequency for all other controlled drugs should be determined by the standard of practice in the community and under the circumstances of the pharmacy.

26. I am the PIC of a pharmacy that is so small there are no other staff. Do I still have to complete a reconciliation report, or is the perpetual inventory sufficient?

Yes. All pharmacies, regardless of size or staff, that stock federal Schedule II controlled substances must comply with CCR 1715.65.

27. I work in a chain pharmacy, where we store the data used to perform the reconciliation at the corporate level and keep a signed face sheet in the pharmacy. Are the acquisition and disposition records used to complete the reconciliation report required to be attached to the reconciliation/signature page?

Attachment is not mentioned in the regulation, but as referenced in 1715.65(c)(4), all records used to compile each inventory reconciliation report shall be maintained in the pharmacy or clinic for at least three years in a readily retrievable form. The board recommends all documents related to compilation of an inventory reconciliation report be stored together.

CALIFORNIA HOSPITAL ASSOCIATION

Providing Leadership in Health Policy and Advocacy

DATE: October 17, 2019

TO: Medication Safety Committee Members

FROM: BJ Bartleson, MS, RN, NEA-BC, Vice President, Nursing & Clinical Services

SUBJECT: Biosimilars

SUMMARY

In light of the 2018 concerns, when Aetna designated Fulphila as the preferred biosimilar for cancer patients who are at risk for febrile neutropenia, CHA has established an internal team and work plan to assess, monitor and understand member, health plan, and other association and related stakeholder issues, (See Biosimilars Overview, Attachment, #1). The issue represents a utilization management action that undermines the clinical judgement of providers. This is an emerging issue that may escalate, and CHA is developing a CHA Medication Safety sub-committee of affected members to monitor and explore the issue. Attached (Attachment #2) is a list of oncology centers we have developed to begin to identify affected or potentially affected members.

Rita Shane from Cedars has been taking the lead and has been communicating these concerns with the Board of Pharmacy. The attached summary describes the issues to date.

DISCUSSION

1. Are there any other committee member hospitals that wish to join the sub-committee?
2. Are there any additional Oncology Centers we need to add to the list?
3. Are there other issues/advice the committee can offer us?

ACTION REQESTED

- Informational

Attachments: Health Plan Designation of Preferred Biosimilars Work Plan
California Cancer Centers

BJB:br

Health Plan Designation of Preferred Biosimilars Work Plan

Biosimilars – Overview

In fall 2018, CHA was made aware of concerns with Aetna's recent designation of Fulphila as the preferred biosimilar for cancer patients who are at risk for febrile neutropenia (low white blood count leading to hospitalization due to risk of life-threatening infections).

- Biosimilar drugs are considered therapeutically equivalent, however, because they are made from living organisms, there is a risk of an immune reaction if patients are switched from one product to another. Therefore, the decision should be under the purview of the medical staff to ensure the safety of the medication prescribed. The interchangeability of a product is for a clinician to determine.
- While plans routinely choose preferred drugs related to self-administered drugs in the outpatient setting, once a patient is admitted into a hospital, the formulary is determined by the hospital or health system. The decision-making authority for which drugs are used for hospital patients are defined by regulatory agencies (The Joint Commission, CMS Conditions of Participation, CDPH). More specifically, the selection of drugs in a hospital setting is under the purview of a hospital's Pharmacy and Therapeutics Committee, as required under state regulation.
- This is not a prior authorization issue; there is concern the plan should not dictate which brands of drugs hospitals are required to stock and administer.
- There are significant patient safety concerns. A requirement to have a specific biosimilar available based on the patient's health plan would require significant resources to procure, store, label, and dispense the payer-specific biosimilar to the patient. There are currently 11 biosimilars approved in the U.S. with 188 more in development and 260 approved in some international markets. If this became the standard, the additional time involved to order, store, label and pick the right payer-specific drug would add complexity to these processes. This consequence would be a significant increase in the risk of harmful medication errors by adding more steps to the medication management processes.
- There are significant operational, financial, safety and revenue compliance (different billing codes for different products) implications if payers designate which biosimilar products hospitals should use. Since each biosimilar has a different code for billing, if there is a mix-up of drugs, and the payer-specific biosimilar is not the one that is given, the payer would deny the payment and the patient would be responsible for paying the full cost of the medication.
- In addition, most health systems belong to group purchasing organizations, so the health system decides what's on their formulary and the group purchasing organization decides on how to contract for the drugs.

Health Plan Engagement: Aetna

On Nov. 13, 2018, CHA met with Delia D. Johnson, Director of Compliance, California Market, Aetna and her team to discuss member concerns regarding Aetna's policy, including the lack of clarity regarding precertification requirements for pharmaceuticals being focused on the outpatient care setting. Aetna indicated it had not received similar feedback prior to our call. Aetna was unwilling to rescind its policy.

Stakeholder Engagement:

- State Regulatory Agencies
    - **California Department of Managed Health Care (DMHC) –** On Dec. 19, 2018, CHA met with DMHC to discuss the policy. DMHC shared that they would work with Aetna to better understand the policy. DMHC agreed that the policy is confusing but thinks this is largely a contracting issue. The best DMHC thought they could do is get the policy implementation delayed and have Aetna place more clear parameters around the policy (i.e. clarify that this only applies in the outpatient settings, that continuity of care provisions apply). The Knox-Keene Act already requires health plans to provide coverage for medically necessary prescription drugs, including non-formulary drugs determined to be medically necessary.

      On Jan. 11, DMHC confirmed that Aetna would be issuing a clarification to the policy in their monthly "Office Notes" publication to reflect that the prior authorization requirement for G-CSF products applies to outpatient services. If the patient has started a course of treatment while inpatient, providers should note this in the precertification request so Aetna can apply their continuity of care policies. Aetna confirmed this on Jan. 11 as well.

      The clarification was included in the March 2019 Provider Newsletter, available at https://www.aetna.com/health-care-professionals/newsletters-news/office-link-updates/state-specific-ca-march-2019/clarification-g-csf-products.html.

Additional Resources:

- Congressional Research Services Report - *Biologics and Biosimilars: Background and Key Issues (Updated June 6, 2019)*: https://fas.org/sgp/crs/misc/R44620.pdf
- Amgen Biosimilars – *Biosimilars Update: 2019 Report (Sixth Edition):* https://www.amgenbiosimilars.com/pdfs/2019%20Trends%20in%20Biosimilars%20Report%20Electronic%20Version%20-%20USA-BIO-80182.pdf
- July 2019 Vizient Drug Price Forecast: https://www.vizientinc.com/Our-solutions/Pharmacy-Solutions/Drug-Price-Forecast-public
- Center for Biologics article - UnitedHealthcare Names 3 Biosimilars Preferred Treatments in 2019 MA Plans: https://www.centerforbiosimilars.com/news/unitedhealthcare-names-3-biosimilars-preferred-treatments-in-2019-ma-plans

CA Cancer Centers							
Type	**Institution Name**	**Center Name**	**Contact**	**Degree**	**Title**	**Address**	**Phone**
Basic	Salk Institute	Salk Institute Cancer Center	Reuben Shaw	PhD	Director	10010 North Torrey Pines Rd. La Jolla, CA 92037	858-453-4100
Basic	Sanford Burnham Prebsy Medical Discovery Institute	Sanford Burnham Prebsy Medical Discovery Institute	Garth Powis	PhD	Director	10010 North Torrey Pines Rd. La Jolla, CA 92037	858-646-3100
Comp	Beckman Research Institute	City of Hope Comprehensive Cancer Center	Steven Rosen	MD, FACP	Director	1500 East Duarte Road Duarte, CA 1010-3000	626-471-7300
Comp	Stanford University	Stanford Cancer Institute	Steven Artandi	PhD, MD	Director	Lokey Research Building MC 5466 265 Campus Drive Suite G2103 Stanford, CA 94305-5796	650-736-1808
Comp	University of California Los Angeles	Jonsson Comprehensive Cancer Center	Michael A. Teitell	MD, PhD	Director	8-684 Factor Building 10833 Le Conte Avenue Los Angeles, CA 90095-1781	310-825-5268
Comp	University of California, Davis	UC Davis Comprehensive Cancer Center	Primo N. Lara	MD	Director	4501 X Street Suite 3003 Sacramento, CA 95817	916-734-5800
Comp	University of California, Irvine	Chao Family Comprehensive Cancer Center	Richard A. Van Etten	MD, PhD	Director	101 The City Dirve Building 56, Rt. 81 Room 209 Orange, CA 92868	714-456-6310
Comp	University of California, San Diego	Moores Comprehensive Cancer Center	Scott Lippman	MD, PhD	Director	5833 Health Sciences Drive MC 0658 La Jolla, CA 92093-0658	858-822-1222
Comp	University of California, San Francisco	UCSF Helen Diller Family Comprehensive Cancer Center	Alan Ashworth	PhD, FRS	Director	1450 3rd Street UCSF Box 0128 San Francisco, Ca 94143	415-476-5876
Comp	University of Southern California	USC Norris Comprehensive Cancer Center	Caryn Lerman	MD	Director	1441 Eastlake Ave. Los Angeles, 90089-9181	323-865-0816

CALIFORNIA HOSPITAL ASSOCIATION

Providing Leadership in Health Policy and Advocacy

DATE: October 17, 2019

TO: Medication Safety Committee Members

FROM: BJ Bartleson, MS, RN, NEA-BC, VP Nursing & Clinical Services

SUBJECT: Medication Safety Tool Review

SUMMARY

It is time for the items in the Medication Safety Tool to be reviewed and updated. Attached is a speadsheet outlining the tools, workgroup and last action.

ACTION REQUESTED

- Review and update.

Attachments: Medication Safety Tool Spreadsheet

BJB:br

Medication Safety Tools - Update			7/11/2019
Tool Title	**Workgroup**	**Date Finalized**	**Last Action**
Anticoagulant Tool (Parts I and II)	Sarah Stephens, Dan Ross, BJ Bartleson	2017	
ED Management	Jeannette Hanni, BJ Bartleson, Rory Jaffe	not finalized	Jeannette to review and finalize
Improving Safe Opioid Tools	Dan Ross, Vicki Ferraresi	not finalized	Dan Ross had comments on the latest version - not finalized.
Insulin Safe Practice	Eddie Avedikian, Dan Ross Jonathan Nelson	2017	
Medication Reconciliation	Rita Shane (infographic)	2017	
Nusing Sterile Compounding	BJ Bartleson, Lori Nolan	not finalized	October 2018 meeting BJ Bartleson and Lori Nolan to create a workgroup
Reducing Adverse Drug Events (ADEs)	no workgroup assigned	not finalized	this was not part of the original toolkit plan
Reducing Controlled Substance Diversion in Hospitals	Rita Shane, Candace Fong, Jeannette Hanni, Amy Gutierrez	2017	
Sterile Compounding		2018	
Track and Trace Law FAQs	Doug O'Brien	not finalized	Doug to update with new law info.
Additional information outside of committee work			
Drug Product Shortages	outside references		
High Alert Medication Tools	outside references		
Improving Safe Opioid Use	outside references		
Nusing Sterile Compounding	outside reference		needs updated

CALIFORNIA HOSPITAL ASSOCIATION

Providing Leadership in Health Policy and Advocacy

DATE: October 17, 2019

TO: Medication Safety Committee Members

FROM: BJ Bartleson, MS, RN, NEA-BC, Vice President, Nursing & Clinical Services
Jeannette Hanni, R.Ph, MPA, FCSHP, Committee Co-Chair
Candace Fong, Pharm.D., Committee Co-Chair

SUBJECT: CSHP Presentation

SUMMARY

CHA was asked to present on CHA's Medication Safety Committee at the Annual CSHP Conference. Attached is the power point that will be presented by Co-Chair Jeannette Hanni.

CHA appreciates the opportunity to present at this conference as well as being able to host a quarterly face to face meeting during the conference time.

ACTION REQESTED

- Information only

Attachments: CSHP Presentation

BJB:br

California Hospital Association Medication Safety Committee

An interagency, interdisciplinary committee for safe medication use.

Jeannette Hanni, R.Ph., M.P.A., FCSHP
Co-Chair, CHA Medication Safety Committee

1

Program Objectives:

- Be able to describe the CHA Medication Safety Committee's Mission and Purpose
- Be able to describe the relationship between State Pharmacy/Health Agencies and the CHA Medication Safety Committee
- Be able to describe the role of CSHP in the formation and success of the Committee
- Be able to list some key best practice guidelines produced by the CHA Medication Safety Committee

2

Regulatory Environment 2009

The CHA Medication Safety Committee was formed in December, 2009 in response to the challenging regulatory environment of the time.

3

Patient Safety Legislation in CA

2001/2002
- Senate Bill 1875 SB 801
- All general acute care hospitals, surgical clinics, and special hospitals
- Adopt a plan to eliminate or substantially reduce medication – related errors

2006
- Senate Bill 1301
- System in place for early detection of, and response to, systemic problems that cause adverse healthcare events leading to death or serious disability

2007
- California Department of Public Health
- "All facility Letter"–
- Mandatory Reporting of adverse events

2008
- Notification of the intent to survey to monitor facility implementation of their CDPH approved MERP (medication error reduction plan) in 2009

4

Genesis of the Med Safety Committee

- Medication errors and medication safety became a very important focus of both CDPH and BoP
- Communication and interactions between regulatory bodies and facilities were strained, as fines and citations were increasing
- Top leadership at CHA and CDPH began conversations about the new legislation and the resulting hospital experiences
- The CDPH Deputy Director approaches CHA about hosting an interagency, interdisciplinary medication safety committee composed of various agencies and health care organizations in 2009

5

CHA Medication Safety Committee

Mission

"The mission of the Medication Safety Committee is to provide leadership within the health care community to promote the highest standards related to the safe and effective use of medications"

6

CHA Medication Safety Committee

Purpose

The purpose of the Medication Safety Committee is to provide a forum for diverse multi-disciplinary health care organizations, that include health care delivery organizations, patient safety organizations, discipline specific professional association/organizations and regulatory agencies, to promote safe medication practices in the state of California. The Committee will focus on acting as a source of medication safety expertise, providing a venue for the coordination of medication safety activities and making recommendations related to medication safety legislation and regulations.

7

Committee Membership

- Co-Chairs (2)
- Members (13)
- Advisory/Ex-Officio (9)
- Staff (2)*
- The Committee consists of 16-35 representatives

*BJ Bartleson, RN, MS, NEA-BC
Vice President Nursing and Clinical Services
California Hospital Association
1215 K St., Sacramento, CA
bjbartleson@calhospital.org

8

Guidelines for Membership:

1. Demonstrated expertise in medication safety and understanding of regulatory environment based on current or recent job responsibilities
2. Contributions to medication safety at the organization and/or professional level
3. Practice experience related to medication safety and regulatory compliance: at least 3 years (preferred).

9

Guidelines for membership, cont

- Representatives are chosen from large hospital systems, public institutions, private facilities, free-standing facilities, small and rural facilities, university/teaching facilities and specialty facilities.
- Representatives from other state agencies or CHA committees
- Initial membership was appointed by CHA staff
- Subsequent membership is submitted for Committee approval
- Two co-chairs lead the committee

10

State Agency and Professional Association Membership Cohort

- California Department of Public Health
- California Society of Health System Pharmacists
- California Board of Pharmacy
- Centers for Medicare and Medicaid Services
- Collaborative Alliance for Nursing Outcomes
- Association of California Nurse Leaders California
- California Medical Association
- California HQI and California Hospital Patient Safety Organization (CHPSO)
- Risk Management Association

11

CHA Committee Membership Cohort

- Representatives from the following CHA committees/centers:
  - Center for Behavioral Health
  - Rural Health Center
  - Hospital Quality Institute
  - Certification and Licensing Committee
  - Center for Hospital Medical Executives
  - EMS/Trauma Committee
  - Hospital-Based Outpatients Clinics Workgroup
  - Center for Post Acute Care
  - Case Management Committee
  - Governance Forum

12

Medication Safety Committee
Hospital Representation
BY COUNTY
As of July 17, 2019

13

Members and Member Hospitals

Contact	Position Type	Represented Organization	County (Represented Or
Candace Fong, Pharm.D	Chair	Dignity Health	San Francisco
Jeanette Hanni, R.Ph, MPA, FCSHP	Chair	Sutter Health	Sacramento
Amy Gutierrez, PharmD	Member	Kaiser Permanente	Alameda
Carolyn Brown, RN, MS	Member	Santa Clara Valley Medical Center	Santa Clara
Deepak Sisodiya, PharmD, MHA	Member	Stanford Health Care	Santa Clara
Diana Schultz, RPh, MHSA	Member	Palomar Medical Center Escondido	San Diego
Doug O'Brien, Pharm.D	Member	Kaiser Foundation Hospitals	Sacramento
Eddie W. Avedikian, PharmD	Member	Providence Holy Cross Medical Center	Los Angeles
Kathy Ghomeshi, Pharm.D, MBA, BCPS, CPPS	Member	UCSF Medical Center	San Francisco
Kevin Dorsey Tyler, MD, PhD	Member	Enloe Medical Center - Esplanade Campus	Butte
Lori Nolan-Mullenhour, MSN, RN, NE-BC, CEN	Member	Providence Little Company of Mary Medical Center Torrance	Los Angeles
Nasim Karmali, RPh	Member	Kaiser Permanente Redwood City Medical Center	San Mateo
Richard B. Rabens, MD, MPH, FAAP	Member	Kaiser Permanente	Alameda
Rita Shane, Pharm.D, FASHP, FCSHP	Member	Cedars-Sinai Medical Center	Los Angeles
Sarah Stephens, Pharm. D, BCPS, CPPS	Member	Kaweah Delta Health Care District	Tulare
Anne Sodergren	Ex-officio	California Board of Pharmacy	
Art Woo, Pharm.D	Ex-officio	California Department of Public Health	
Cari Lee, Pharm.D	Ex-officio	California Department of Public Health	
John Christensen, Pharm.D	Ex-officio	California Department of Public Health	
Kimberly Kirchmeyer	Ex-officio	Medical Board of California	
Loriann DeMartini, Pharm.D	Ex-officio	California Society of Health System Pharmacists	
Patti Owens	Ex-officio	California Association of Health Facilities	
Randy Kajioka, Pharm.D	Ex-officio	California Correctional Health Care Systems	
Steve Thompson	Ex-officio	California Society of Health System Pharmacists	

14

Committee Member Responsibilities

- Provide hospital-industry leadership to the Committee and CHA Board of Trustees
- Identify issues and develop possible solutions and best practices to improve the safety of the medication use process
- Work cooperatively with key stakeholders to develop creative solutions.
- Provide communication to member hospitals regarding medication safety issues.
- Maintain/increase awareness of the legislative and regulatory environment with regard to medication safety issues.

15

Key Interdisciplinary Roles of the Committee

- Inter-agency cooperation and problem solving
- Inter-facility problem solving and sharing
- Advocating for inter-facility best practices
- Multi-facility joint public comment document submissions to various agencies:
  - Board of Pharmacy Sterile Compounding Regulations
  - USP 797/800
  - CDPH/CMS regulations
  - Joint Commission proposed standards changes

16

Subcommittees and Workgroups

- The MERP subcommittee
- The Hospital Emergency Department subcommittee
- The High-Risk High-Alert Medications subcommittee
- CURES
- Sterile Compounding
- Nursing Sterile Compounding
- SB 1254 – Medication Profiles

17

Agency Report Outs: Board of Pharmacy and CDPH

- MERP/GACHRLS (medication error reduction plan) and common findings
- Current BoP legislation, regulatory actions, and future plans
- Opportunities to gain insight and to provide feedback regarding survey findings and process
- Opportunities to provide the health care community with tools to prevent future findings and to improve patient safety.
- To standardize the survey process and address the issue of surveyor drift/inconsistency

18

CHA Legislative Report

CHA summarizes the list of current legislative endeavors related to medications in order to:

- Determine the Committee's position on each important bill
- Determine what actions the Committee should take to effect change or to support/oppose a specific bill.
- Determine what tools, subcommittees and/or communications the Committee should undertake to facilitate a proposed or completed piece of legislation for its CHA members

19

CSHP Report

The CSHP President and/or CEO updates the Committee on:

- Current and future educational opportunities
- Plans for Seminar and other conferences
- Joint CSHP/CHA efforts on subcommittee work
- Joint communications efforts
- Legislative endeavors and the CSHP position on key bills

20

Committee Work Product

Guidelines, Resources and Research

21

CHA Website

22

CHA Medication Safety Toolkit

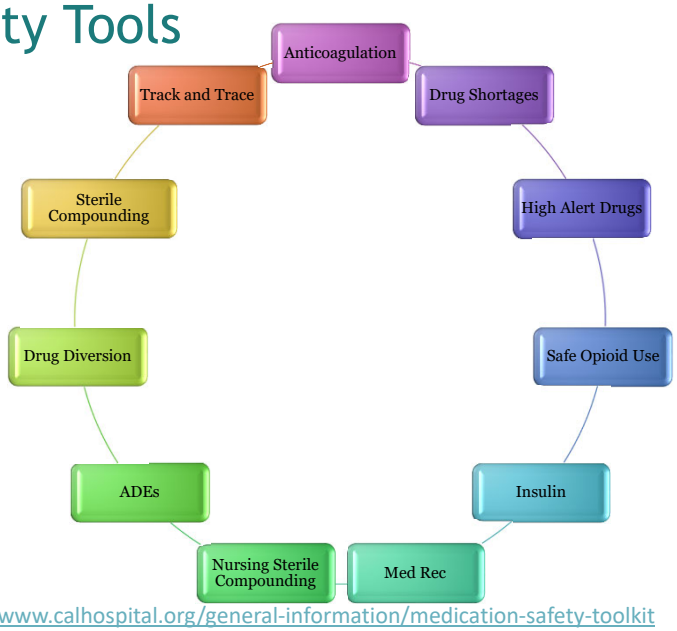
"This toolkit contains tools that have been developed and recommended by the CHA Medication Safety Committee for hospital and health care providers to use as they evaluate current practices and develop specific programs around these key medication safety topics. The tools are not fixed protocols that must be followed, nor are they entirely inclusive or exclusive of all methods of reasonable care that can obtain/produce the same results. Additional reference items and websites have been added under respective tool tabs."*

https://www.calhospital.org/general-information/medication-safety-toolkit

* Tools are currently being updated

23

Safety Tools



https://www.calhospital.org/general-information/medication-safety-toolkit

24

Anticoagulants:

Step	Actions to Consider To Increase Medication Safety		
	Heparin	**Warfarin**	**Low Molecular Weight Heparin**
Pharmacy Purchasing, Storage and Product Labeling	• Purchase commercially available, standard concentrations of IV heparin infusions for use throughout the facility. • Restrict purchases and storage of premixed IV solutions to the pharmacy if feasible • Limit the variety of concentrations and sizes purchased both for large volume parenterals and vials of heparin. Consider eliminating 10,000 units/ml vials • Store away from other drugs in the pharmacy with look alike names or packaging. Use TALLman lettering on labels and bins to differentiate between HeSpan and hEParin • Clearly differentiate heparin products used for treatment from low concentration products such as flushes. • Purchase patient population specific strengths of prefilled heparin flush syringes (e.g. Peds) • Use Tallman lettering on labels, order screens, MARs and other documents when feasible	• Purchase from a single manufacturer to promote consistent bioavailability for this narrow therapeutic index drug	• Purchase commercially available doses in prefilled syringes

25

Anticoagulants, continued

	Heparin	**Warfarin**	**Low Molecular Weight Heparin**
Pharmacy Dispensing	• Heparin orders are verified by pharmacy prior to dispensing	• Doses are provided in unit dose packaging. • Consider elimination of pill splitting on nursing units	
	Common considerations • If available, use machine readable bar coding for verification prior to dispensing from the pharmacy for refill of automated dispensing cabinets or for single patient use		
	Heparin	**Warfarin**	**Low Molecular Weight Heparin**
Administration	• Conduct an independent verification of 5 "rights", drug concentration, rate of infusion, pump channel selection, IV line labeling and attachment is conducted prior to administration and at change in therapy • Use infusion pumps, preferably smart pumps with error reduction software, for IV infusions • Use smart pumps to deliver bolus and continuous doses from the same container only when a bolus dose can be safely programmed (with hard limits on total dose and minimum infusion time), and the pump automatically converts to continuous infusion after bolus is delivered. Be mindful of the volume required for bolus doses	• Consider MAR[8] documentation of pertinent lab values used to monitor therapy (e.g. INR[3]) • Schedule warfarin administration for the same time each day after INR[3] results are available (afternoon or early evening)	• Conduct an independent verification of 5 "Rights" and correct indication prior to administration • Rotate and document injection sites • Monitor injection sites for hematomas • Use initial weight for weight based dosing. Do not adjust weight each day • To avoid the loss of drug when using the 30 and 40 mg prefilled syringes, do not expel the air bubble from the syringe before the injection.

26

Anticoagulant Tool Sections:

Pharmacy Purchasing, Storage and Product Labeling	Patient Care Unit Storage	Prescribing	Pharmacist Order Entry Process
Pharmacy Dispensing	Administration	Education	Monitoring
Other Considerations	Transitional Care: Discharge Planning	References	Resource Tools

27

28

Sterile Compounding Grids

- The California Society of Health-System Pharmacists (CSHP) and the California Hospital Association (CHA) have partnered together to provide the following grids to our membership.

Sterile Compounding Grids:

- Competency and Training Grid
- Compounding Frequency of Documentation and Cleaning Grid
- Facilities and Engineering Controls Requirements Grid (Non-Hazardous)
- Facilities and Engineering Controls Grid (Hazardous)
- Garbing Grid (Hazardous)
- Garbing Grid (Non-Hazardous)
- Required Environmental, Personnel & End Product Testing Grid
- Temperature Requirements and Monitoring Grid

Additional Resources:

- Donning, Hygiene & Doffing for Sterile Compounding (Hazardous)
- Donning, Hygiene & Doffing for Sterile Compounding (Non-Hazardous)
- OSHPD Sterile Compounding Pharmacies for Hospital Facilities (Advisory Guide)

29

CALIFORNIA HOSPITAL ASSOCIATION
Leadership in Health Policy and Advocacy

Facilities and Engineering Controls: Hazardous Drugs

CHA/CSHP Interpretation of California Board of Pharmacy (1/1/17) and USP <800> Pending Requirements

CSHP CALIFORNIA SOCIETY OF HEALTH-SYSTEM PHARMACISTS

BOARD OF PHARMACY REGULATIONS CCR§1735 Effective January 1, 2017				
SECONDARY ENGINEERING CONTROL	**PRIMARY ENGINEERING CONTROL**	**Beyond Use Dates**		**Comments**
		LOW RISK	**MEDIUM RISK**	
• **Temp 20-24C (68-75F)** • **Externally vented** • **HEPA filtered air** • **Negative pressure** • **Physically separate room**	• **PECs ISO Class 5 Negative Pressure unidirectional flow** • **HEPA filtered airflow** • **Non-turbulent** • **HEPA filtered exhausted air** • **External venting should be dedicated to one BSC or CACI**	• **Sterile to sterile** • **=< 3 commercial packages** **=< 2 entries into 1 sterile container**	• **Combine or pool sterile ingredients** • **For multiple patients or one patient multiple times** • **Complex manipulations** • **Long compounding process**	
• **ISO Class 7 or better** • Sink in ante area • At least 0.01"-0.03" w.c. negative relative to all adjacent space (rooms, above ceiling and corridors) • Minimum 30 Air Changes Per Hour (ACPH) • Ante-area ISO 7 or better CCR §1735.6(e)	• Biological Safety Cabinet, Class II Type A2 • Biological Safety Cabinet, Class II Type B2 • Compounding Aseptic Containment Isolators (CACI) with unidirectional flow. Air within the CACI shall not be recirculated or turbulent. CACI must meet requirements in 1751.4 (f) (1-3)	48 hours at Room Temp* 14 days at Cold Temp** 45 days Solid Frozen State ***	30 hours at Room Temp* 9 days at Cold Temp** 45 days Solid Frozen State ***	• Document daily Pressure Differential or air velocity, or use continuous recording device, between adjoining ISO rooms. 1751.1(a)(8) • Requires negative pressure ISO 5 PEC 1751.4(g) • Each ISO environment requires certification by a CETA certified vendor at least every 6 months CCR §1751(b)(1), 1751.4(f) • Externally vented 1751.4(g), 1735.6(e) • All surfaces within the room shall be smooth, seamless, impervious, and non-shedding 1735.6(e)(4)
• **Segregated Compounding Area** • Sterile to sterile compounding only • Sink at least 3 ft from PEC • Minimum of at least 3 ft line of demarcation around PEC • Emergency eye wash station acceptable • At least 0.01"-0.03" w.c. negative relative to all adjacent space (rooms, above ceiling and corridors) • Minimum 12 ACPH 1735.6 (e) (1)	• Biological Safety Cabinet, Class II Type A2 • Biological Safety Cabinet, Class II Type B2 • Compounding Aseptic Containment Isolators (CACI) with unidirectional flow. Air within the CACI must not be recirculated or turbulent CACI must meet requirements in 1751.4 (f) (1-3)	12 hours	NA	• Requires negative pressure ISO 5 PEC 1751.4(g) • Each ISO environment requires certification by a CETA certified vendor at least q 6 months CCR §1751(b)(1), 1751.4(f)(g) • Externally vented 1751.4(g), 1735.6(e) • All surfaces within the room shall be smooth, seamless, impervious, and non-shedding 1735.6(e)(4) • Sink can be within 3 ft of CACI if CACI meets requirements in 1751.4 (f) (1-3)

This tool is intended for hospital and health care pharmacists in charge (PICs) and senior staff as they evaluate their current sterile compounding practices. The tool is not a fixed compliance assessment that must be followed and should not be construed as legal advice or used to resolve legal problems.

Last Revised 9/17/2018

Page **1** of **2**

30

Key Accomplishments to Date:

Collaborative Relationships

- Created and fostered a dynamic relationship between CHA member facilities and California regulatory agencies
- Created a healthy environment to discuss the issues of the day as it relates to medication use

Legislative Advocacy

- Submitted numerous "public comment period" letters with suggested language changes for sterile compounding regulations
- SB 1254 Medication Profiles legislation passed in 2019

Member Advocacy and Education

- Joint CSHP/CHA Sterile Compounding Task Force
- Collaborated on the second edition of the CSHP/CHA Sterile Compounding Tools
- Created several best practice guidelines related to; opioids, controlled substances, insulin, etc.

31

Conclusion

- This inter-agency, multidisciplinary committee for safe medication use was first convened in December, 2009. The Committee is composed of state regulators and licensing boards, professional societies and associations, quality organizations for healthcare, and practitioners from many different practice settings. Members serve voluntarily at the appointment of the California Hospital Association. The members provide leadership within the health care community to promote the highest standards related to the safe and effective use of medications.

32

33

CALIFORNIA HOSPITAL ASSOCIATION

Providing Leadership in Health Policy and Advocacy

DATE: October 17, 2019

TO: Medication Safety Committee Members

FROM: BJ Bartleson, MS, RN, NEA-BC, Vice President, Nursing & Clinical Services

SUBJECT: Title 22 Pharmacy Pre-Regulatory All Facilities Letter (AFL-19-27) For Pharmaceutical Regulations (§ 70261 - §70269)

SUMMARY

CDPH issued AFL 19-27 (Attachment #1), Notice of Stakeholder Meeting for General Acute Care Hospital Clinical Laboratory, Pharmaceutical, and dietetic Services Regulations. The stakeholder meeting requested hospitals respond to specific questions, as well as advise on additional information relative to the regulatory sections. The questions were:

1) Under what circumstances would it be beneficial to allow practitioners to prescribe drugs in hospitals, and which practitioners?
2) Who conducts medical reconciliation for high-risk patients upon admission to the hospital?
3) What are the drawbacks or benefits that may result from requiring the person taking a verbal or telephone order for drugs to record the name of the person calling in the order for the prescriber (the caller) as well as their own name (the person inscribing the verbal or telephone order), and allowing the pharmaceutical service to accept electronic signatures?
4) What are the drawbacks or benefits that may result from requiring a retrospective review of any drugs administered pursuant to a standing order (without a patient-specific prescription), and requiring the medical necessity for administering drugs pursuant to a standing order be documented in the patient's medical record?
5) What are the drawbacks or benefits that may result from requiring drug storage temperature logs to be maintained and readily available for three years?
6) What would be the drawbacks and benefits of requiring hospitals licensed pursuant to section 4029 of the Business and Professions Code to provide office space for the Director of pharmaceutical service? What would be the drawbacks and of requiring hospitals licensed pursuant to section 4029 of the business and professions Code that have pharmacy managers to provide office space for the pharmacy manager, while allowing offices to be shared if there are multiple pharmacy managers?

We received three responses back to the questions, (See Attachment #2), including additional information from one member on specific regulatory sections.

In 2011, CHA submitted regulatory comments to CDPH to assist in their pre-regulatory review and update of Title 22 GACH sections. Attachment #3 highlights the 2011 recommended revisions and the 2019 comments we received for AFL 19-27 response.

DISCUSSION

1. What thoughts do members have on the 2011 and the 2019 comments?
2. Are there additional comments you'd like to add or change to the specific regulatory sections or general questions?

ACTION REQESTED

- Finalize comments for CHA submittal

Attachments: AFL 19-27
Comment Table
Regulation Table

BJB:br

Susan Fanelli
Acting Director

State of California—Health and Human Services Agency
California Department of Public Health

GAVIN NEWSOM
Governor

August 18, 2019

AFL 19-27

TO: General Acute Care Hospitals

SUBJECT: Notice of Stakeholder Meeting for General Acute Care Hospital Clinical Laboratory, Pharmaceutical, and Dietetic Services Regulations

All Facilities Letter (AFL) Summary

This AFL notifies facilities that the California Department of Public Health (CDPH), Center for Health Care Quality (CHCQ) is holding a stakeholder meeting on August 30, 2019, to discuss general acute care hospital (GACH) clinical laboratory, pharmaceutical, and dietetic services regulations.

CDPH is holding a stakeholder meeting to discuss updating the GACH clinical laboratory, pharmaceutical and dietetic services regulations. The meeting will be held at:

Date	August 30, 2019
Time	2:00 PM to 3:30 PM
Location	1500 Capitol Avenue Training Room C Sacramento, CA 95814

CDPH would like to discuss and hear your ideas for updating regulations for these GACH services. Please come to the meeting prepared to share your comments and suggestions after reviewing the “Questions for Stakeholder Engagement – Clinical Laboratory, Pharmaceutical, and Dietetic Services”.

There is limited seating, so if you are attending in-person, please reserve your seat by August 23, 2019, by emailing CHCQRegulationsUnit@cdph.ca.gov. If you are attending via WebEx, please register with the WebEx Registration link. When choosing an audio connection, select “I will call in.”

Please check the Regulation Stakeholder Meetings webpage for updates and opportunities to comment. If you have any questions about this AFL, please email CHCQRegulationsUnit@cdph.ca.gov.

Sincerely,

Original signed by Heidi W. Steinecker

Heidi W. Steinecker
Deputy Director

Attachments:
“Questions for Stakeholder Engagement – Clinical Laboratory, Pharmaceutical, and Dietetic Services” (PDF)
“Existing Title 22 Clinical Laboratory, Pharmaceutical, and Dietetic Service Regulations” (PDF)

Center for Health Care Quality, MS 0512 . P.O. Box 997377 . Sacramento, CA 95899-7377
(916) 324-6630 . (916) 324-4820 FAX
Department Website (cdph.ca.gov)

Page Last Updated : August 15, 2019

Hospital responses to questions+A1:D4D3A1:D5A1:D5AA1:D9		**AFL 19-27 - Pharmacy**	
Question	**Hospital 1 Response**	**Hospital 1 Recommendation**	**Hospitals 2 & 3 Responses**
1. Under what circumstances would it be beneficial to allow practitioners to prescribe drugs in hospitals, and which practitioners?	Business & Professions Code (BPC) 4052.1 and 4052.2 permit pharmacists in licensed health care facilities such as a GACH to initiate and adjust drug regimen in accordance with policies/procedures/protocols. Thus, the GACH Pharmaceutical Services regulations should be updated to align with BPC regulations and allow pharmacists to prescribe drugs in hospitals under circumstances defined in policies, procedures, and protocols approved by the Pharmacy and Therapeutics Committee	Revise 70263.g as follows No drugs shall be administered except by licensed personnel authorized to administer drugs and upon the order of a person lawfully authorized to prescribe or furnish. This shall not preclude the administration of aerosol drugs by respiratory therapists. The order shall include the name of the drug, the dosage and the frequency of administration, the route of administration, if other than oral, and the date, time and signature of the prescriber or furnisher. Orders for drugs should be written or transmitted *by ~~the prescriber or furnisher~~ a person lawfully authorized to prescribe or furnish and shall be recorded in the patients' medical record. This includes practitioners such as pharmacists who may prescribe or furnish drug based on the patient's diagnosis under a policy, procedure or protocol approved by the pharmacy and therapeutics committee or its equivalent.* Verbal orders for drugs shall be given only by a person lawfully authorized to prescribe or furnish and shall be recorded promptly in the patient's medical record, noting the name of the person giving the verbal order and the signature of the individual receiving the order. The prescriber or furnisher shall countersign the order within 48 hours.	1. Licensed practitioners who have been credentialed, competency checked, approved by Medical Staff to practice within their scope of practice. They must be willing and able to adhere to the hospital policies and procedures for patient and medication safety and regulatory purposes. Physicians with nonstaff privileges if authorized by the Medical Staff office may prescribe in the outpatient setting only within their scope of practice. 2. It is beneficial as it is a core function of care within a hospital.
2. Who conducts medical reconciliation for high-risk patients upon admission to the hospital?	Senate Bill 1254 and BPC 4118.5 require a hospital pharmacist, a trained intern pharmacist, or a trained pharmacy technician in hospitals with a licensed bed capacity of less than 100 beds, to obtain accurate medication profile or list for high-risk patients upon admission based upon criteria established in approved policies and procedures. In addition, medication reconciliation may be conducted by a pharmacist, physician, or allied-health professional. The Pharmaceutical Services regulations should be amended to reflect current regulations and the updated BPC regulations regarding medication profiles for high-risk patients.	Add new section in 70263 *Medication reconciliation shall be completed by a pharmacist, prescriber or allied health professional. A pharmacist, trained intern pharmacist, or trained pharmacy technician shall obtain a medication profile or list for each high-risk patient upon admission. The hospital shall establish criteria regarding who is a high-risk patient and determine the timeframe for completion of the medication profile or list* .	1. Only Licensed Independent Practitioners should conduct medical reconciliation. Medication history for high risk patients (defined as transplant patients and patients on oral anticoagulants) is taken by Pharmacy Technicians specially trained in medication history. 2. Pharmacy personnel performs this function.

Question	Hospital 1 Response	Hospital 1 Recommendation	Hospitals 2 & 3 Responses
3. What are the drawbacks or benefits that may result from requiring the person taking a verbal or telephone order for drugs to record the name of the person calling in the order for the prescriber (the caller) as well as their own name (the person inscribing the verbal or telephone order), and allowing the pharmaceutical service to accept electronic signatures?	70263.g limits the use of verbal orders to person lawfully authorized to prescribe or furnish medications and should remain unchanged to limit individuals involved in the verbal/telephone order process and potential errors. Verbal and telephone orders are utilized in cases of emergency or when requiring the prescriber to write or enter an order would be associated with a delay in patient care or potential patient harm. However, these orders continue to be associated with transcription and administrations errors which can be compounded when there is an intermediary added to the process who obtains the order from the original prescriber and relays it to the person who will ultimately act upon it. Requiring documentation of the name of the person calling in the order for the prescriber can improve the root cause analysis process when responding to a medication error. The person who called in the order on behalf of the prescriber may be able to provide additional information as to factors that may have contributed to the error. On the other hand, this additional documentation requirement may unknowingly encourage the use of intermediaries in the verbal/telephone order process and increase errors.	**No changes to 70263.g**	1. Benefit: accountability and traceability. Drawbacks: transcription errors resulting from verbal or telephone orders 2. Drawback is the increased incidence of verbal based errors. The benefit is that in rare occasions prescribers cannot access computers to dial into the EMR to place orders, necessitating a verbal route.
4. What are the drawbacks or benefits that may result from requiring a retrospective review of any drugs administered pursuant to a standing order (without a patient-specific prescription), and requiring the medical necessity for administering drugs pursuant to a standing order be documented in the patient's medical record	Requiring a retrospective review of drugs administered pursuant to a standing order or documentation of medical necessity appears to be redundant to already established safety processes, may increase documentation and auditing without yielding additional safety benefits for patients. Per 70263.h, standing orders for drugs may only be used under specific circumstances and patient medical conditions (or necessity for administration) and must be approved initially and annually by the Pharmacy and Therapeutics Committee or its equivalents to ensure they are based on current nationally recognized and evidence-based guidelines and recommendations. In addition, per Health & Safety Code 1339.63, each GACH is required to evaluate and address medication-related errors to prevent them from occurring. This required process would capture errors related to standing orders and help ensure deficiencies identified are remedied.	**No changes to 70263.h**	Benefits: QAPI. Drawbacks: time-consuming and labor intensive to perform chart review

Question	Hospital 1 Response	Hospital 1 Recommendation	Hospitals 2 & 3 Responses
5. What are the drawbacks or benefits that may result from requiring drug storage temperature logs to be maintained and readily available for three years?	Temperature logs are used to ensure that medications are stored per manufacturer's recommendations until they are administered to patients. Requiring record retention of temperature logs for 3 years may be burdensome for facilities based on the volume of records generated and the space required to retain them. However, in case of a reported adverse event or other patient complaint where medication potency is questioned, having historical temperature logs to refer to would be beneficial in the investigation or complaint resolution process.	Revise 70263.q.6 to add subsection (i): *i. Drug storage temperature logs shall be maintained and readily available for three years.*	1. Drawbacks: many temperature logs are documented on paper format. Three-year requirement posts significant challenge on storage, archiving and retrieving of record. Converting to electronic format requires major capital investment and training. 2. Benefit is that it supports the monitoring of temperature controls for drug stability. It should not be required as readily available but retrievable within 3 days.
6. What would be the drawbacks and benefits of requiring hospitals licensed pursuant to section 4029 of the Business and Professions Code to provide office space for the Director of the pharmaceutical service? What would be the drawbacks and benefits of requiring hospitals licensed pursuant to section 4029 of the Business and Professions Code that have pharmacy managers to provide office space for the pharmacy manager, while allowing offices to be shared if there are multiple pharmacy managers?	The Director and manager(s) of pharmaceutical oversee not only complex medication use processes and related quality and safety issues, they also manage the financial, regulatory, operational and human resources aspects of the department which frequently entails handling of confidential/sensitive information. In order to carry out these responsibilities effectively while maintaining confidentiality as required, dedicated space is needed. Hospitals are often challenged with space as they expand services and patient populations served, however, allocating space for the director or manager(s) of pharmaceutical services is critical.	Add new section (c) to 70269: *(c) Adequate office space shall be provided for the Chief Pharmacy Officer, Pharmacy Executive or equivalent position and pharmacy managers* .	1. a. to provide office space for the Director of the pharmaceutical service: benefits include the necessity to conduct private meetings with external customers as well as internal employees for performance-related or confidential discussions to meet employee's needs. Drawbacks: none as this is a basic necessity to run a pharmacy department. b. to provide office space for the pharmacy manager, while allowing offices to be shared if there are multiple pharmacy managers? Drawbacks of office spaced shared by multiple managers: managers will lose the means to conduct private one-on-one confidential or performance related discussions with employees. In addition, confidential information (employees' salaries, raises, and disciplinary notes) are not protected if office space is shared by other managers. Benefits: none 2. Office space should always be allocated to managers as a workspace for performance of their administrative duties. Office space for personnel managers should be private to allow for counseling staff. Office space for Directors should always be private and not shared due to the nature of their duties.

AFL	Article	Section	2011 Recommended Revisions	2011 Reason	2019 Recommended Revisions	2019 Reason
19-27	**Article 3**	§ 70241. Clinical Laboratory Service Definition.	No Changes.			
19-27	**Article 3**	§ 70243 (a) Clinical Laboratory Service General Requirements.	Recommend adding "all applicable state and federal laws."	The codes specified change and new state and federal laws are added to existing regulations.		
19-27	**Article 3**	§ 70243 (d) and (e) Clinical Laboratory Service General Requirements.	Move administrative policy regulations to a general section in Article 3 related to such issues common to all basic service areas.	Drafting a standard set of general requirements relevant to all basic services, and including nuanced requirements pertaining to a specific service area under the section pertaining to that service area, will eliminate redundancy, improve consistency, and focus attention to key provisions that are unique to a particular basic service.		
19-27	**Article 3**	§ 70243 (f) (1) through (8) Clinical Laboratory Service General Requirements.	Sub-section 70243 (f) should be replaced with: "The Director of the Clinical Laboratory shall fulfill his/her duties in accordance with Federal Clinical Laboratory Improvement Amendments 88 regulations."	Harmonization with federal requirements will eliminate confusion and bring about consistency.		
19-27	**Article 3**	§ 70243 (g) Clinical Laboratory Service General Requirements.	No Changes.		No drugs shall be administered except by licensed personnel authorized to administer drugs and upon the order of a person lawfully authorized to prescribe or furnish. This shall not preclude the administration of aerosol drugs by respiratory therapists. The order shall include the name of the drug, the dosage and the frequency of administration, the route of administration, if other than oral, and the date, time and signature of the prescriber or furnisher. Orders for drugs should be written or transmitted by ~~the prescriber or furnisher~~ a person lawfully authorized to prescribe or furnish and shall be recorded in the patients' medical record. This includes practitioners such as pharmacists who may prescribe or furnish drug based on the patient's diagnosis under a policy, procedure or protocol approved by the pharmacy and therapeutics committee or its equivalent. Verbal orders for drugs shall be given only by a person lawfully authorized to prescribe or furnish and shall be recorded promptly in the patient's medical record, noting the name of the person giving the verbal order and the signature of the individual receiving the order. The prescriber or furnisher shall countersign the order within 48 hours. (Cedars)	
19-27	**Article 3**	§ 70243 (j) Clinical Laboratory Service General Requirements.	Move administrative policy regulations to a general section in Article 3 related to such issues common to all basic service areas.	Drafting a standard set of general requirements relevant to all basic services, and including nuanced requirements pertaining to a specific service area under the section pertaining to that service area, will eliminate redundancy, improve consistency, and focus attention to key provisions that are unique to a particular basic service.		
19-27	**Article 3**	§ 70245 (a) Clinical Laboratory Service Staff.	No Changes.			
19-27	**Article 3**	§ 70247 (b) Clinical Laboratory Service Equipment and Supplies.	Eliminate "Such facilities shall be inspected at appropriately short intervals each day of the week to assure these requirements are being fulfilled"	Outdated and unnecessary.		

AFL	Article	Section	2011 Recommended Revisions	2011 Reason	2019 Recommended Revisions	2019 Reason
19-27	**Article 3**	§ 70249. Clinical Laboratory Service Space.	Reference Title 24	In regards to space requirements, hospitals are subject to Title 22 and Title 24 regulations. This duplication is confusion, cumbersome and inefficient. CHA recommends that space requirements be eliminated from Title 22 and only contained in Title 24. If, for operational reasons, Title 22 needs to differ from Title 24 space requirements, L&C should specify why this difference is necessary and substantiate why the requirements need to overlay those already required by OSHPD.		
19-27	**Article 3**	§ 70261. Pharmaceutical Service Definition.	No Changes.			
19-27	**Article 3**	§ 70263. Pharmaceutical Service General Requirements.	It is strongly encouraged that The Joint Commission requirements are cross referenced with this entire section to ensure the language is either similar or does not contain conflicting requirements.	To avoid conflicting requirements.		
19-27	**Article 3**	§ 70263 (b) Pharmaceutical Service General Requirements.	Section 70263 (b) pertaining to the responsibility and accountability of the pharmaceutical service needs to be amended to state that there is to be a single pharmacist responsible for the day-to-day activities of the pharmacy. This person could be referred to as the Director or Manager or other equivalent.	There needs to be a single pharmacist responsible for the day-to-day activities of the pharmacy. This person could be referred to as the Director or other equivalent.		
19-27	**Article 3**	§ 70263 (c) Pharmaceutical Service General Requirements.	Section 70263 (c) should be amended to explicitly state that the Director of Pharmacy needs to be a member of the Pharmacy and Therapeutics Committee as opposed to “one pharmacist.”	This is a global statement outlining the minimum responsibilities for the pharmacy and therapeutics committee. The functions of the pharmacy will be responsible to the medical staff via the Pharmacy and Therapeutics Committee.		
19-27	**Article 3**	§ 70263 (f) (2) and (3) Pharmaceutical Service General Requirements.	Sections 70263 (f) (2) and (3) needs language added allowing technicians to assume these responsibilities.	These changes will allow pharmacy technicians and interns, who are well-trained and qualified, to conduct monthly inspections. The use of technicians and interns for this task will free up time for pharmacists to address patient care activities.	The *emergency* supply shall be inspected by a pharmacist, *intern pharmacist, or pharmacy technician* at periodic intervals established in written policies. Such inspections shall occur ~~*no less frequently than every 30 days*~~ *at least monthly* . Records of such inspections shall be kept for at least three years. (Cedars)	· BPC 4119.6 allows intern pharmacists to conduct inspections of the drug supply. BPC 4115(i) allows pharmacy technicians to package emergency supplies, seal emergency containers, and perform monthly checks of drug supplies. Allowing pharmacy technicians to inspect the emergency supply would align with BPC 4115(i)(3). • Revising the frequency for inspection of the emergency supply from “no less frequently than every 30 days” to “at least monthly” would align with 70263.Q(10), BPC 4119.7c, and BPC 4115i (3) for inspection of all medications within the facility at least monthly.

AFL	Article	Section	2011 Recommended Revisions	2011 Reason	2019 Recommended Revisions	2019 Reason
19-27	**Article 3**	§ 70263 (g) Pharmaceutical Service General Requirements.			No drugs shall be administered except by licensed personnel authorized to administer drugs and upon the order of a person lawfully authorized to prescribe or furnish. This shall not preclude the administration of aerosol drugs by respiratory therapists. The order shall include the name of the drug, the dosage and the frequency of administration, the route of administration, if other than oral, and the date, time and signature of the prescriber or furnisher. Orders for drugs should be written or transmitted ~~by the prescriber or furnisher~~ a person lawfully authorized to prescribe or furnish and shall be recorded in the patients' medical record. This includes practitioners such as pharmacists who may prescribe or furnish drug based on the patient's diagnosis under a policy, procedure or protocol approved by the pharmacy and therapeutics committee or its equivalent. Verbal orders for drugs shall be given only by a person lawfully authorized to prescribe or furnish and shall be recorded promptly in the patient's medical record, noting the name of the person giving the verbal order and the signature of the individual receiving the order. The prescriber or furnisher shall countersign the order within 48 hours. (Cedars)	
19-27	**Article 3**	§ 70263 (k) Pharmaceutical Service General Requirements.	In the era of prescriber computer order entry, section 70263 (k) needs to be amended to add language that allows electronic data transmission with electronic signature (physician order entry).	Adds use of electronic data transmission with electronic signature (physician order entry)		
19-27	**Article 3**	§ 70263 (l) Pharmaceutical Service General Requirements.			Medications shall not be left at the patient's bedside ~~*unless the prescriber so orders*~~ *unless permitted by written policies and procedures which include the dispensing, storage, and records of use of bedside medications. These policies and procedures shall be approved by the pharmacy and therapeutics committee or equivalent* . Such bedside medications shall be kept in a cabinet, drawer or in possession of the patient. Drugs shall not be left at the bedside which are listed in Schedules II, III and IV of the Federal Comprehensive Drug Abuse Prevention and Control Act of 1970 as amended. ~~*If the hospital permits bedside storage of medications, the pharmacy and therapeutics committee or equivalent shall approve written policies and procedures for the dispensing, storage and records of use, of such medications*~~ (Cedars)	Requiring a physician order to allow medications to be at bedside when there is already an approved policy appears redundant with no added improvement in patient safety. As long as the pharmacy and therapeutics committee has evaluated and approved the list of medication to be stored at bedside, an order to dictate bedside storage is unnecessary.

AFL	Article	Section	2011 Recommended Revisions	2011 Reason	2019 Recommended Revisions	2019 Reason
19-27	**Article 3**	§ 70263 (m) (1-3) Pharmaceutical Service General Requirements.			(m) Medications brought by or with the patient to the hospital shall not be administered to the patient unless all the following conditions are met: (1) The drugs have been ordered by a person lawfully authorized to give such an order and the order entered in the patient's medical record. *(2) The medication containers are clearly and properly labeled.* (3) The contents of the containers have been examined and *the medication can be* positively identified, after arrival at the hospital, by the patient's prescriber or the hospital pharmacist. (Cedars)	To improve medication adherence, patients often transfer their medications from their original container to more convenient and ubiquitous containers. If the medication can be identified by the pharmacist and is in congruence with the order, medications brought from home should be used even if they are not stored in clearly and properly labeled containers. Requiring the use of medications from home that are only stored in clearly and properly labeled containers may be associated with delays in care if the medication cannot be readily supplied by the hospital (e.g. non-formulary medications, limited distribution medications, REMS medications).
19-27	**Article 3**	§ 70263 (n) Pharmaceutical Service General Requirements.			The hospital shall establish a supply of medications which is accessible without entering either the pharmacy or drug storage room during hours when the pharmacist is not available. Access to the supply shall be limited to designated registered nurses *and healthcare professionals who may administer medications under their scope of practice* . Records of drugs taken from the supply shall be maintained and the pharmacist shall be notified of such use. The records shall include the name and strength of the drug, the amount taken, the date and time, the name of the patient to whom the drug was administered and the signature of the *healthcare professional* ~~*registered nurse*~~ . The pharmacist shall be responsible for maintenance of the supply and assuring that all drugs are properly labeled and stored. The drug supply shall contain *the* ~~*that*~~ type and quantity of drugs necessary to meet the immediate needs of patients as determined by the pharmacy and therapeutics committee. (Cedars)	Besides registered nurses, other healthcare professionals are allowed per their scope of practice to administer medications and may need to access the pharmacy or drug storage room when the pharmacist is unavailable. This include but is not limited to respiratory therapists or imaging technicians. Limiting access to registered nurses may be associated in delays in care and adverse patient outcomes in areas of hospitals where nurses are not readily available, but medications need to be administered in a timely fashion.
19-27	**Article 3**	§ 70263 (o) Pharmaceutical Service General Requirements.			Investigational drug use shall be in accordance with applicable state and federal laws and regulations and policies adopted by the hospital. Such drugs shall be used only under the ~~*direct*~~ supervision of the principal investigator *or designee* , who shall be a member of the medical staff and be responsible for assuring that informed consent is secured from the patient. Basic information concerning the dosage form, route of administration, strength, actions, uses, side effects, adverse effects, interactions and symptoms of toxicity of investigational drugs shall be *readily* available ~~*at the nursing station*~~ where such drugs are being administered and in the pharmacy. The pharmacist shall be responsible for the proper labeling, storage and distribution of such drugs pursuant to the written order of the investigator. (Cedars)	· Patients may be admitted to hospitals and need to continue therapy with investigation drugs issued at a different institution or by a principal investigator not able to directly supervise the care of the patient. As long as the hospital has access to the investigational drug monograph, the signed informed consent, and the patient is under the care of a member of the medical staff, direct supervision by the principal investigator is not necessary to ensure safety. • The medication monograph can be available to nurses either physically at the nursing station or electronically.

AFL	Article	Section	2011 Recommended Revisions	2011 Reason	2019 Recommended Revisions	2019 Reason
19-27	**Article 3**	§ 70263 Pharmaceutical Service General Requirements. (New Section)				
19-27	**Article 3**	§ 70263 (q)(6) Pharmaceutical Service General Requirements. Add subsection (i)			*i. Drug storage temperature logs shall be maintained and readily available for three years. (Cedars)*	Temperature logs are used to ensure that medications are stored per manufacturer's recommendations until they are administered to patients. Requiring record retention of temperature logs for 3 years may be burdensome for facilities based on the volume of records generated and the space required to retain them. However, in case of a reported adverse event or other patient complaint where medication potency is questioned, having historical temperature logs to refer to would be beneficial in the investigation or complaint resolution process.
19-27	**Article 3**	§ 70265. Pharmaceutical Service Staff.	No Comments made to date		A pharmacist shall have overall responsibility for the pharmaceutical service. *The pharmacist* ~~*He*~~ shall be responsible for the procurement, storage and distribution of all drugs as well as the development, coordination, supervision and review of pharmaceutical services in the hospital. Hospitals with a limited permit shall employ a pharmacist on at least a consulting basis. Responsibilities shall be set forth in a job description or agreement between the pharmacist and the hospital. The pharmacist shall be responsible to the administrator and shall furnish *the administrator with* ~~*him written*~~ reports and recommendations regarding the pharmaceutical services within the hospital *on an ongoing basis* . ~~*Such reports shall be provided no less often than quarterly.*~~ (Cedars)	· Change from 'He/Him' to gender neutral term. • Given the critical nature of the quality and safety issues the Director of the pharmaceutical services handle, there should be ongoing dialogue with hospital administrators regarding pharmaceutical services. Quarterly written reports are insufficient and inadequate in ensuring hospital administrators remain informed.
19-27	**Article 3**	§ 70267. Pharmaceutical Service Equipment and Supplies.	No Comments made to date			
19-27	**Article 3**	§ 70269. Pharmaceutical Service Space.	Reference Title 24	In regards to space requirements, hospitals are subject to Title 22 and Title 24 regulations. This duplication is confusion, cumbersome and inefficient. CHA recommends that space requirements be eliminated from Title 22 and only contained in Title 24. If, for operational reasons, Title 22 needs to differ from Title 24 space requirements, L&C should specify why this difference is necessary and substantiate why the requirements need to overlay those already required by OSHPD.		
19-27	**Article 3**	§ 70269. (b) Pharmaceutical Service Space.			All spaces and areas used for the storage of drugs shall be ~~*lockable*~~ *secure* and accessible to authorized personnel only. (Cedars)	Drug storage spaces can either be secure with a physical lock or the continuous presence of authorized personnel who monitors access.

AFL	Article	Section	2011 Recommended Revisions	2011 Reason	2019 Recommended Revisions	2019 Reason
19-27	**Article 3**	§ 70269. Pharmaceutical Service Space. Add new section (c)			*(c) Adequate office space shall be provided for the Chief Pharmacy Officer, Pharmacy Executive or equivalent position and pharmacy managers. (Cedars)*	The Director and manager(s) of pharmaceutical oversee not only complex medication use processes and related quality and safety issues, they also manage the financial, regulatory, operational and human resources aspects of the department which frequently entails handling of confidential/sensitive information. In order to carry out these responsibilities effectively while maintaining confidentiality as required, dedicated space is needed. Hospitals are often challenged with space as they expand services and patient populations served, however, allocating space for the director or manager(s) of pharmaceutical services is critical.
19-27	**Article 3**	§ 70269. (d) Pharmaceutical Service Space. Add new section (d)			Hospitals that must undergo facilities changes in order to meet regulations are considered compliant by the enforceable implementation date as long as a plan and timeline are in place to resolve identified deficiencies. (Cedars)	Several upcoming regulations (e.g. USP 797 and 800) require major changes to hospital facilities to ensure compliance. However, these changes often require permits and other approvals (e.g. OSHPD, local city permits) before they can be initiated, throughout the process and before final use of the space. These requirements are outside of the control of the hospital. Allowing hospitals that have a defined plan for facilities changes to remain in compliance would support the intent of the regulations while allowing for the time necessary to safely and legally make changes to facilities.

AB 149 **(Cooper D) Controlled substances: prescriptions.**

Status: 3/11/2019-Approved by the Governor. Chaptered by Secretary of State - Chapter 4, Statutes of 2019.

Summary: Current law classifies certain controlled substances into designated schedules. Current law requires prescription forms for controlled substance prescriptions to be obtained from security printers approved by the department, as specified. Current law requires those prescription forms to be printed with specified features, including a uniquely serialized number. This bill would delay the requirement for those prescription forms to include a uniquely serialized number until a date determined by the Department of Justice that is no later than January 1, 2020. The bill would require, among other things, the serialized number to be utilizable as a barcode that may be scanned by dispensers.

CHA Position	Priority	Lobbyist	Issues	CHA Subject
S		AH, MS*	BJ*, LR	Pharmacy

AB 387 **(Gabriel D) Task force: adverse drug events: prescriptions.**

Status: 8/30/2019-Failed Deadline pursuant to Rule 61(a)(12). (Last location was APPR. SUSPENSE FILE on 8/19/2019)(May be acted upon Jan 2020)

Summary: Would create the Prescription Labeling and Adverse Drug Event Prevention Advisory Task Force, with membership as prescribed, to develop information, make recommendations, and report findings to the California State Board of Pharmacy, the Medical Board of California, and the Legislature on matters relating to the inclusion of the condition or purpose for which a drug is prescribed on prescription labels and adverse drug events.

CHA Position	Priority	Lobbyist	Issues	CHA Subject
F		KAS*, MS	BJ	Medical Staff-Physician and Peer Review, Pharmacy

AB 528 **(Low D) Controlled substances: CURES database.**

Status: 9/26/2019-Enrolled and presented to the Governor at 4 p.m.

Summary: Would, on and after January 1, 2021, require a dispensing pharmacy, clinic, or other dispenser to instead report the information required by the CURES database no more than one working day after a controlled substance is released to a patient or a patient's representative, except as specified. The bill would similarly require the dispensing of a controlled substance included on Schedule V to be reported to the department using the CURES database. The bill would make conforming changes to related provisions.

CHA Position	Priority	Lobbyist	Issues	CHA Subject
F		MS	BJ	Pharmacy

AB 690 **(Aguiar-Curry D) Pharmacies: relocation: remote dispensing site pharmacy: pharmacy technician: qualifications.**

Status: 9/5/2019-Enrolled and presented to the Governor at 3 p.m.

Summary: Would authorize relocation of a pharmacy that is destroyed or severely damaged as a result of a natural disaster or due to events that led to a declared federal, state, or local emergency, if no changes are made to the management and control, or ownership, of the pharmacy, and all applicable laws and regulations are followed, and require that the board be notified of the relocation immediately upon identification of the new location. The bill would specify the qualifications for a registered pharmacy technician to work at a remote dispensing site pharmacy, relating to licensing, certification, education, and minimum work experience, including completion of at least 2,000 hours of experience within the previous 2 years.

CHA Position	Priority	Lobbyist	Issues	CHA Subject
F		MS	BJ	Pharmacy

AB 714 **(Wood D) Opioid prescription drugs: prescribers.**

Status: 9/5/2019-Approved by the Governor. Chaptered by Secretary of State - Chapter 231, Statutes of 2019.

Summary: Current law requires a prescriber, as defined, to offer to a patient a prescription for naloxone hydrochloride or another drug approved by the United States Food and Drug Administration for the complete or partial reversal of opioid depression when certain conditions are present, including if the patient presents with an increased risk for overdose or a history of substance use disorder, and to provide education on overdose prevention to patients receiving a prescription and specified other persons. This bill would make those provisions applicable only to a patient receiving a prescription for an opioid or benzodiazepine medication, and would make the provisions specific to opioid-induced respiratory depression, opioid overdose, opioid use disorder, and opioid overdose prevention, as specified. The bill, among other exclusions, would exclude from the above-specified provisions requiring prescribers to offer a prescription and provide education prescribers when ordering medications to be administered to a patient in an inpatient or outpatient setting.

CHA Position	Priority	Lobbyist	Issues	CHA Subject
S		AH, MS*	BJ	Pharmacy

AB 824 **(Wood D) Business: preserving access to affordable drugs.**

Status: 9/24/2019-Enrolled and presented to the Governor at 3:30 p.m.

Summary: Would provide that an agreement resolving or settling, on a final or interim basis, a patent infringement claim, in connection with the sale of a pharmaceutical product, is to be presumed to have anticompetitive effects if a nonreference drug filer receives anything of value, as defined, from another company asserting patent infringement and if the nonreference drug filer agrees to limit or forego research, development, manufacturing, marketing, or sales of the nonreference drug filer's product for any period of time, as specified. The bill would provide various exceptions to this prohibition, including, among others, if the agreement has directly generated procompetitive benefits and the procompetitive benefits of the agreement outweigh the anticompetitive effects of the agreement. The bill would make a violation of these provisions punishable by a civil penalty that is recoverable only in a civil action brought by the Attorney General, as specified. The bill would provide that a violator is liable for any other remedies available under the Cartwright Act, the Unfair Practices Act, or the unfair competition law. The bill would require a cause of action to enforce those provisions be commenced within 4 years after the course of action accrued. The bill would define various terms for these purposes.

CHA Position	Priority	Lobbyist	Issues	CHA Subject
F		AH, MS*	BJ	Pharmacy

AB 973 **(Irwin D) Pharmacies: compounding.**

Status: 8/30/2019-Approved by the Governor. Chaptered by Secretary of State - Chapter 184, Statutes of 2019.

Summary: Would require the compounding of drug preparations by a pharmacy for furnishing, distribution, or use to be consistent with standards established in the pharmacy compounding chapters of the current version of the United States Pharmacopeia-National Formulary, including relevant testing and quality assurance. The bill, by imposing a new requirement on pharmacies, the violation of which would be a crime, would impose a state-mandated local program. The bill would authorize the board to adopt regulations to impose additional standards for compounding drug preparations.

CHA Position	Priority	Lobbyist	Issues	CHA Subject
F		AH, MS*	BJ	Pharmacy

AB 1468 **(McCarty D) Opioid Prevention and Rehabilitation Act.**

Status: 9/6/2019-Read third time and amended. Ordered to third reading.

Summary: Would, commencing with the 2021–22 fiscal year, require a manufacturer or wholesaler, as defined, that sells or distributes opioid drugs in this state to submit to the State Department of Public Health a report, including specified information, that details all opioid drugs sold or distributed in this state during the preceding fiscal year. The bill would, commencing with the 2021–22 fiscal year, require the department, in consultation with the board, to calculate the ratable share of a manufacturer or wholesaler, which is the individual portion of the collective sum of $50,000,000 or a lesser amount, as specified, to be paid by the manufacturers and wholesalers, based on the information reported, without double-counting the opioid drug if both a manufacturer and a wholesaler sold or distributed the drug in this state.

CHA Position	Priority	Lobbyist	Issues	CHA Subject
F		MS	BJ	Pharmacy

AB 1803 **(Committee on Health) Pharmacy: health care coverage: claims for prescription drugs sold for retail price.**

Status: 7/12/2019-Approved by the Governor. Chaptered by Secretary of State - Chapter 114, Statutes of 2019.

Summary: The Pharmacy Law requires a pharmacy to inform a customer at the point of sale for a covered prescription drug whether the retail price is lower than the applicable cost-sharing amount for the prescription drug, except as specified, and, if the customer pays the retail price, requires the pharmacy to submit the claim to the customer's health care service plan or health insurer. This bill would instead make the provision requiring the pharmacy to submit the claim to the health care service plan or health insurer operative on January 1, 2020. The bill would also repeal a provision that is similar to the provision being amended by the bill.

CHA Position	Priority	Lobbyist	Issues	CHA Subject
F		AH, MS*	AK	Medi-Cal Managed Care, Pharmacy

ACR 105 **(Chiu D) Prescription drug prices.**

Status: 8/28/2019-Re-referred to Com. on HEALTH.
Summary: This measure would state the Legislature's commitment to lower the cost of prescription drugs for all Californians and to support the expansion of California's single-purchaser system for prescription drugs, and would encourage the Governor to engage with the States of Washington and Oregon and others who wish to partner with our state to lower prescription drug prices across the nation.

CHA Position	Priority	Lobbyist	Issues	CHA Subject
PR		MS	BJ	Pharmacy

SB 159 **(Wiener D) HIV: preexposure and postexposure prophylaxis.**
Status: 9/18/2019-Enrolled and presented to the Governor at 4 p.m.
Summary: Would authorize a pharmacist to furnish preexposure prophylaxis and postexposure prophylaxis in specified amounts and would require a pharmacist to furnish those drugs if certain conditions are met, including that the pharmacist determines the patient meets the clinical criteria for preexposure prohylaxis or postexposure prophylaxis consistent with federal guidelines. The bill would require a pharmacist, before furnishing preexposure prophylaxis or postexposure prophylaxis, to complete a training program approved by the board. Because a violation of these requirements would be a crime, this bill would impose a state-mandated local program.

CHA Position	Priority	Lobbyist	Issues	CHA Subject
F		MS	BJ	Pharmacy

SB 377 **(McGuire D) Juveniles: psychotropic medications: medical information.**
Status: 9/19/2019-Enrolled and presented to the Governor at 3 p.m.
Summary: Current law requires the Medical Board of California to review specified data provided by the State Department of Health Care Services and the State Department of Social Services regarding Medi-Cal physicians and their prescribing patterns of psychotropic medications and related services for dependents and wards of the juvenile court in order to determine if any potential violations of law or excessive prescribing of psychotropic medications inconsistent with the standard of care exist and, if warranted, to conduct an investigation. This bill would require, by September 1, 2020, the forms developed by the Judicial Council to include a request for authorization by the child or the child's attorney to release the child's medical information to the Medical Board of California in order to ascertain whether there is excessive prescribing of psychotropic medication inconsistent with a specified standard of care.

CHA Position	Priority	Lobbyist	Issues	CHA Subject
F		AH*, MS	LR, SL*	Chemical/Substance Abuse, Pharmacy

SB 569 **(Stone R) Controlled substances: prescriptions: declared local, state, or federal emergency.**
Status: 9/10/2019-Enrolled and presented to the Governor at 4 p.m.
Summary: Would authorize a pharmacist, during a declared local, state, or federal emergency pursuant to which the California State Board of Pharmacy issues a notice that the board is waiving the application of the provisions of the Pharmacy Law, to fill a prescription for a controlled substance for use by a patient who cannot access medications as a result of the declared local, state, or federal emergency, regardless of whether the prescription form meets the above-specified requirements, if certain other requirements are met, including that the prescription is written and dispensed within the first 2 weeks of the notice issued by the board.

CHA Position	Priority	Lobbyist	Issues	CHA Subject
S		AH, MS*	BJ	Pharmacy

SB 624 **(Wilk R) Qualified medical supplies providers: sales taxes: repayment.**
Status: 5/16/2019-May 16 hearing: Held in committee and under submission.
Summary: Would provide a procedure for a qualified medical supplies provider to submit a claim for qualified repayments, as defined, with the California Department of Tax and Fee Administration, as provided. The bill would define a qualified medical supplies provider to mean a pharmacy or durable medical equipment provider enrolled in Medi-Cal who, among other things, paid sales taxes imposed under the Sales and Use Tax Law and the California Constitution for sales of medical supplies or equipment furnished to Medi-Cal beneficiaries occurring during the period beginning June 1, 2011, and before November 1, 2013, for which a portion of payments from Medi-Cal for those sales, which included applicable sales tax reimbursement, was paid back to the State Department of Health Care Services by the pharmacy or durable medical equipment provider due to the reduction of Medi-Cal payment by specified law.

CHA Position	Priority	Lobbyist	Issues	CHA Subject
F		AH*, BG	RW	Medi-Cal Managed Care, Pharmacy

SB 642 **(Stone R) Pharmacy benefit management: Prescription Acquisition and Adjudication Agency.**

Status: 4/24/2019-Re-referred to Com. on HEALTH.

Summary: Would, on and after July 1, 2021, prohibit a health care service plan or a health insurer from entering into, renewing, or extending a contract for pharmacy benefit manager services, as specified.

CHA Position	Priority	Lobbyist	Issues	CHA Subject
F		AH*, MS	AK*, BJ	Pharmacy

SB 650 **(Rubio D) Cancer Medication Advisory Committee.**

Status: 8/30/2019-Failed Deadline pursuant to Rule 61(a)(12). (Last location was APPR. SUSPENSE FILE on 8/14/2019)(May be acted upon Jan 2020)

Summary: Would require the California State Board of Pharmacy to establish the Cancer Medication Advisory Committee for the purpose of identifying the best mechanism to enable the transfer of unused cancer medications to persons in need of financial assistance to ensure access to necessary pharmaceutical therapies. The bill would require the committee to be composed of 9 specified members and would require members of the committee to serve without compensation.

CHA Position	Priority	Lobbyist	Issues	CHA Subject
F		AH, MS*	BJ	Pharmacy

SB 655 **(Roth D) Pharmacy.**

Status: 8/30/2019-Approved by the Governor. Chaptered by Secretary of State. Chapter 213, Statutes of 2019.

Summary: The Pharmacy Law provides for the licensing and regulation of pharmacists and pharmacies by the California State Board of Pharmacy in the Department of Consumer Affairs. That law authorizes a pharmacy technician trainee to be placed in a pharmacy to complete an externship for the purpose of obtaining practical training required to become licensed as a pharmacist. That law prohibits the externship from being for a period of more than 120 hours, except if a pharmacy technician trainee's externship involves the rotation between a community pharmacy and a hospital pharmacy, in which case the externship is authorized to be for a period of up to 320 hours. That law prohibits more than 120 hours of the 320 hours from being completed in a community pharmacy setting or in a single department in a hospital pharmacy. This bill would instead require the externship to be for a period of no fewer than 120 hours and no more than 140 hours.

CHA Position	Priority	Lobbyist	Issues	CHA Subject
F		MS	BJ	Pharmacy

Total Measures: 17
Total Tracking Forms: 17

10/4/2019

AB 149 **(Cooper D) Controlled substances: prescriptions.**

Status: 3/11/2019-Approved by the Governor. Chaptered by Secretary of State - Chapter 4, Statutes of 2019.

Summary: Current law classifies certain controlled substances into designated schedules. Current law requires prescription forms for controlled substance prescriptions to be obtained from security printers approved by the department, as specified. Current law requires those prescription forms to be printed with specified features, including a uniquely serialized number. This bill would delay the requirement for those prescription forms to include a uniquely serialized number until a date determined by the Department of Justice that is no later than January 1, 2020. The bill would require, among other things, the serialized number to be utilizable as a barcode that may be scanned by dispensers.

CHA Position	Priority	Lobbyist	Issues	CHA Subject
S		AH, MS*	BJ*, LR	Pharmacy

AB 528 **(Low D) Controlled substances: CURES database.**

Status: 9/26/2019-Enrolled and presented to the Governor at 4 p.m.

Summary: Would, on and after January 1, 2021, require a dispensing pharmacy, clinic, or other dispenser to instead report the information required by the CURES database no more than one working day after a controlled substance is released to a patient or a patient's representative, except as specified. The bill would similarly require the dispensing of a controlled substance included on Schedule V to be reported to the department using the CURES database. The bill would make conforming changes to related provisions.

CHA Position	Priority	Lobbyist	Issues	CHA Subject
F		MS	BJ	Pharmacy

AB 690 **(Aguiar-Curry D) Pharmacies: relocation: remote dispensing site pharmacy: pharmacy technician: qualifications.**

Status: 9/5/2019-Enrolled and presented to the Governor at 3 p.m.

Summary: Would authorize relocation of a pharmacy that is destroyed or severely damaged as a result of a natural disaster or due to events that led to a declared federal, state, or local emergency, if no changes are made to the management and control, or ownership, of the pharmacy, and all applicable laws and regulations are followed, and require that the board be notified of the relocation immediately upon identification of the new location. The bill would specify the qualifications for a registered pharmacy technician to work at a remote dispensing site pharmacy, relating to licensing, certification, education, and minimum work experience, including completion of at least 2,000 hours of experience within the previous 2 years.

CHA Position	Priority	Lobbyist	Issues	CHA Subject
F		MS	BJ	Pharmacy

AB 714 **(Wood D) Opioid prescription drugs: prescribers.**

Status: 9/5/2019-Approved by the Governor. Chaptered by Secretary of State - Chapter 231, Statutes of 2019.

Summary: Current law requires a prescriber, as defined, to offer to a patient a prescription for naloxone hydrochloride or another drug approved by the United States Food and Drug Administration for the complete or partial reversal of opioid depression when certain conditions are present, including if the patient presents with an increased risk for overdose or a history of substance use disorder, and to provide education on overdose prevention to patients receiving a prescription and specified other persons. This bill would make those provisions applicable only to a patient receiving a prescription for an opioid or benzodiazepine medication, and would make the provisions specific to opioid-induced respiratory depression, opioid overdose, opioid use disorder, and opioid overdose prevention, as specified. The bill, among other exclusions, would exclude from the above-specified provisions requiring prescribers to offer a prescription and provide education prescribers when ordering medications to be administered to a patient in an inpatient or outpatient setting.

CHA Position	Priority	Lobbyist	Issues	CHA Subject
S		AH, MS*	BJ	Pharmacy

AB 824 **(Wood D) Business: preserving access to affordable drugs.**

Status: 9/24/2019-Enrolled and presented to the Governor at 3:30 p.m.

Summary: Would provide that an agreement resolving or settling, on a final or interim basis, a patent infringement claim, in connection with the sale of a pharmaceutical product, is to be presumed to have anticompetitive effects if a nonreference drug filer receives anything of value, as defined, from another company asserting patent infringement and if the nonreference drug filer agrees to limit or forego research, development, manufacturing, marketing, or sales of the nonreference drug filer's product for any period of time, as specified. The bill would provide various exceptions to this prohibition, including, among others, if the agreement has directly generated procompetitive benefits and the procompetitive

benefits of the agreement outweigh the anticompetitive effects of the agreement. The bill would make a violation of these provisions punishable by a civil penalty that is recoverable only in a civil action brought by the Attorney General, as specified. The bill would provide that a violator is liable for any other remedies available under the Cartwright Act, the Unfair Practices Act, or the unfair competition law. The bill would require a cause of action to enforce those provisions be commenced within 4 years after the course of action accrued. The bill would define various terms for these purposes.

CHA Position	Priority	Lobbyist	Issues	CHA Subject
F		AH, MS*	BJ	Pharmacy

AB 973 **(Irwin D) Pharmacies: compounding.**

Status: 8/30/2019-Approved by the Governor. Chaptered by Secretary of State - Chapter 184, Statutes of 2019.

Summary: Would require the compounding of drug preparations by a pharmacy for furnishing, distribution, or use to be consistent with standards established in the pharmacy compounding chapters of the current version of the United States Pharmacopeia-National Formulary, including relevant testing and quality assurance. The bill, by imposing a new requirement on pharmacies, the violation of which would be a crime, would impose a state-mandated local program. The bill would authorize the board to adopt regulations to impose additional standards for compounding drug preparations.

CHA Position	Priority	Lobbyist	Issues	CHA Subject
F		AH, MS*	BJ	Pharmacy

AB 1803 **(Committee on Health) Pharmacy: health care coverage: claims for prescription drugs sold for retail price.**

Status: 7/12/2019-Approved by the Governor. Chaptered by Secretary of State - Chapter 114, Statutes of 2019.

Summary: The Pharmacy Law requires a pharmacy to inform a customer at the point of sale for a covered prescription drug whether the retail price is lower than the applicable cost-sharing amount for the prescription drug, except as specified, and, if the customer pays the retail price, requires the pharmacy to submit the claim to the customer's health care service plan or health insurer. This bill would instead make the provision requiring the pharmacy to submit the claim to the health care service plan or health insurer operative on January 1, 2020. The bill would also repeal a provision that is similar to the provision being amended by the bill.

CHA Position	Priority	Lobbyist	Issues	CHA Subject
F		AH, MS*	AK	Medi-Cal Managed Care, Pharmacy

SB 159 **(Wiener D) HIV: preexposure and postexposure prophylaxis.**

Status: 9/18/2019-Enrolled and presented to the Governor at 4 p.m.

Summary: Would authorize a pharmacist to furnish preexposure prophylaxis and postexposure prophylaxis in specified amounts and would require a pharmacist to furnish those drugs if certain conditions are met, including that the pharmacist determines the patient meets the clinical criteria for preexposure prohylaxis or postexposure prophylaxis consistent with federal guidelines. The bill would require a pharmacist, before furnishing preexposure prophylaxis or postexposure prophylaxis, to complete a training program approved by the board. Because a violation of these requirements would be a crime, this bill would impose a state-mandated local program.

CHA Position	Priority	Lobbyist	Issues	CHA Subject
F		MS	BJ	Pharmacy

SB 377 **(McGuire D) Juveniles: psychotropic medications: medical information.**

Status: 9/19/2019-Enrolled and presented to the Governor at 3 p.m.

Summary: Current law requires the Medical Board of California to review specified data provided by the State Department of Health Care Services and the State Department of Social Services regarding Medi-Cal physicians and their prescribing patterns of psychotropic medications and related services for dependents and wards of the juvenile court in order to determine if any potential violations of law or excessive prescribing of psychotropic medications inconsistent with the standard of care exist and, if warranted, to conduct an investigation. This bill would require, by September 1, 2020, the forms developed by the Judicial Council to include a request for authorization by the child or the child's attorney to release the child's medical information to the Medical Board of California in order to ascertain whether there is excessive prescribing of psychotropic medication inconsistent with a specified standard of care.

CHA Position	Priority	Lobbyist	Issues	CHA Subject
F		AH*, MS	LR, SL*	Chemical/Substance Abuse, Pharmacy

SB 569 **(Stone R) Controlled substances: prescriptions: declared local, state, or federal emergency.**

Status: 9/10/2019-Enrolled and presented to the Governor at 4 p.m.

Summary: Would authorize a pharmacist, during a declared local, state, or federal emergency pursuant to which the California State Board of Pharmacy issues a notice that the board is waiving the application of the provisions of the Pharmacy Law, to fill a prescription for a controlled substance for use by a patient who cannot access medications as a result of the declared local, state, or federal emergency, regardless of whether the prescription form meets the above-specified requirements, if certain other requirements are met, including that the prescription is written and dispensed within the first 2 weeks of the notice issued by the board.

CHA Position	Priority	Lobbyist	Issues	CHA Subject
S		AH, MS*	BJ	Pharmacy

SB 655 **(Roth D) Pharmacy.**

Status: 8/30/2019-Approved by the Governor. Chaptered by Secretary of State. Chapter 213, Statutes of 2019.

Summary: The Pharmacy Law provides for the licensing and regulation of pharmacists and pharmacies by the California State Board of Pharmacy in the Department of Consumer Affairs. That law authorizes a pharmacy technician trainee to be placed in a pharmacy to complete an externship for the purpose of obtaining practical training required to become licensed as a pharmacist. That law prohibits the externship from being for a period of more than 120 hours, except if a pharmacy technician trainee's externship involves the rotation between a community pharmacy and a hospital pharmacy, in which case the externship is authorized to be for a period of up to 320 hours. That law prohibits more than 120 hours of the 320 hours from being completed in a community pharmacy setting or in a single department in a hospital pharmacy. This bill would instead require the externship to be for a period of no fewer than 120 hours and no more than 140 hours.

CHA Position	Priority	Lobbyist	Issues	CHA Subject
F		MS	BJ	Pharmacy

Total Measures: 11
Total Tracking Forms: 11

ACETAMINOPHEN:

What It Is, How It's Used, and the Importance of Access

Acetaminophen Prop 65 Briefing Packet

CHPA®

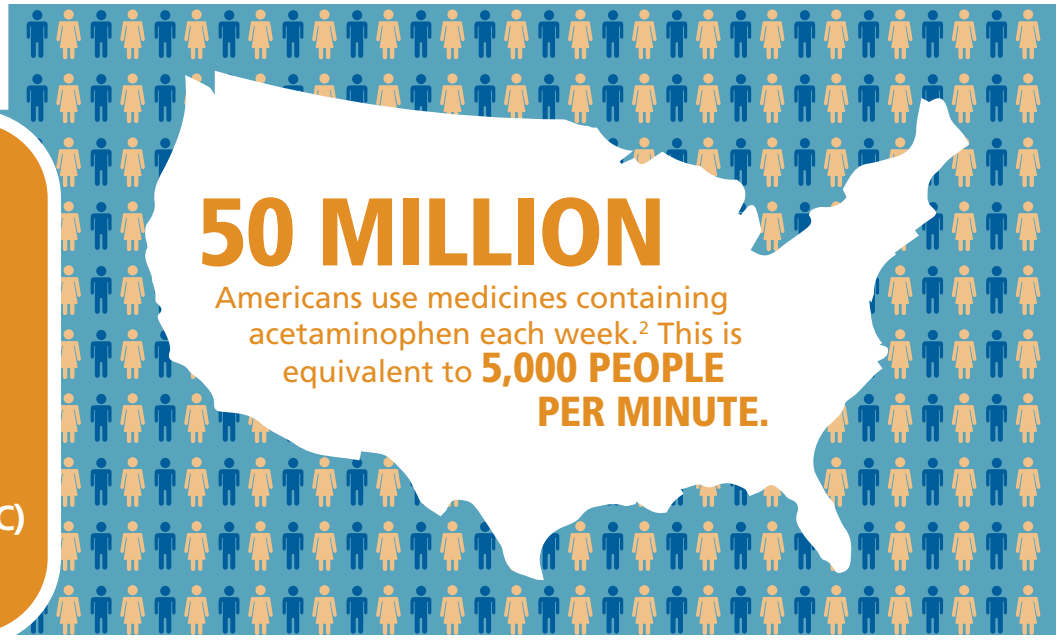
ACETAMINOPHEN

ONE OF THE MOST COMMON DRUG INGREDIENTS IN AMERICA

FOUND IN **MORE THAN**

600

different prescription & over-the-counter (OTC) medicines.[1]



50 MILLION

Americans use medicines containing acetaminophen each week.[2] This is equivalent to **5,000 PEOPLE PER MINUTE.**

SAFE & EFFECTIVE

Results from more than 250 clinical safety and efficacy studies and over six decades of use have proven acetaminophen to be a safe and effective pain reliever and fever reducer, when used as directed.[3]

RECOMMENDED

Acetaminophen has been **identified as either a first-line or preferred OTC pain relief choice for consumers with certain chronic medical conditions** by the:

AMERICAN HEART ASSOCIATION (AHA)
for patients with, or at high risk for, heart disease

NATIONAL KIDNEY FOUNDATION (NKF)
for episodic use in patients with underlying renal disease

AMERICAN GERIATRICS SOCIETY (AGS)
for persistent pain, particularly musculoskeletal pain

AMERICAN COLLEGE OF GASTROENTEROLOGY (ACG)
for patients at risk of peptic ulcer disease

THE SCIENCE

THE SCIENTIFIC EVIDENCE STRONGLY WEIGHS AGAINST CALIFORNIA IDENTIFYING ACETAMINOPHEN AS A KNOWN CARCINOGEN.

1 National Library of Medicine. Pillbox: Identify or Search for a Pill. Bethesda, MD: National Library of Medicine, National Institutes of Health. November 4, 2013. Accessed at: http:// pillbox.nlm.nih.gov

2 Kaufman DW, Kelly JP, Rosenberg L, Anderson TE, Mitchell AA. "Recent Patterns of Medication Use in the Ambulatory Adult Population of the United States: The Sloan Survey." JAMA. 287(3):337-344, 2002. http://jama.jamanetwork.com/article.aspx?articleid=194572

3 Response to Docket No. 1977N-0094L, FDA-Proposed Rule IAAA, McNeil Consumer Healthcare.

What is Prop 65?

Proposition (Prop) 65 (also known as The Safe Drinking Water and Toxic Enforcement Act of 1986), is a state law in California that requires the Office of Environmental Health Hazard Assessment (OEHHA) to publish a list of chemicals known to the state to cause cancer or reproductive harm. OEHHA is required to update the Prop 65 list, which currently includes over 900 substances, at least once a year.

In order to be listed under Prop 65, a chemical must be *"clearly shown through scientifically valid testing according to generally accepted principles"* to cause cancer or reproductive harm. One of the ways that a chemical can be added to the Prop 65 list is if either of two independent advisory committees of scientists and health professionals – the Carcinogen Identification Committee (CIC) or the Developmental and Reproductive Toxicant Identification Committee (DARTIC) – finds that the chemical has been clearly shown to cause cancer or reproductive harm.

Prop 65 is a "right to know law," not a prohibition on chemicals. It establishes a requirement for products to inform consumers that certain chemicals are present which California deems are proven to cause cancer or reproductive harm. Inclusion of a chemical on the Prop 65 list does not ban it. Rather, the law requires that companies provide a *"clear and reasonable"* warning before knowingly and intentionally exposing anyone to a listed chemical. If the exposure is low enough to pose no significant risk of cancer or is well below levels observed to cause reproductive harm, no warning is required.

Acetaminophen is being reviewed by California now because its process emphasizes chemicals with *"widespread exposure."* Next, California's advisory scientists are expected to review the information on acetaminophen and cancer to determine whether acetaminophen should be listed as a carcinogen under Proposition 65. Depending on various factors, a warning statement could be required on labels of products containing acetaminophen.

What is Acetaminophen?

Basic Information

Every day, millions of Americans rely on medicines to improve or maintain their health. One of the most commonly-used drug ingredients in the United States (U.S.) is acetaminophen, also known as paracetamol, a pain reliever and fever reducer found in more than 600 different over-the-counter (OTC) and prescription medicines.[1]

More than 50 million Americans use an acetaminophen-containing medicine each week to treat pain, fever, and minor aches such as those due to the common cold, headache, backache, minor pain of arthritis, toothache, muscular aches, and premenstrual and menstrual cramps.[2]

Medicines Containing Acetaminophen

If an OTC medicine contains acetaminophen, it will be listed on the product package and on the label. Acetaminophen is always prominently written on the front of the box or packaging and will often be highlighted or bolded in the active ingredients section of the Drug Facts label. It is important to know that prescription medicine labels will also list "acetaminophen" or an abbreviation for it (e.g., "APAP," "acetamin," etc.).

COMMON MEDICINE PRODUCTS

THAT MAY CONTAIN ACETAMINOPHEN:

OVER-THE-COUNTER

- Alka-Seltzer Plus®
- Contac®
- Coricidin® HBP
- Dimetapp®
- Excedrin®
- Midol®
- Mucinex®
- NyQuil®/DayQuil®
- Robitussin®
- SUDAFED®
- Theraflu®
- Triaminic®
- TYLENOL®

PRESCRIPTION

- Butalbital
- Endocet®
- Fioricet®
- Hycotab®
- Hydrocet®
- Hydrocodone
- Lortab®
- Oxycodone
- Percocet®
- Phenaphen®
- Sedapap®
- Tramadol
- TYLENOL® with Codeine
- Ultracet®
- Vicodin®

* Acetaminophen is also contained in the generic and store brands of these medicines.
NOTE: This list is just a sample of the more than 600 different medicines that contain acetaminophen.

Benefits of Acetaminophen

Safety and Efficacy Profile

Acetaminophen is one of the most widely-used and thoroughly-studied pain-relieving and fever-reducing medicines, clinically proven over six decades of use and supported by more than 250 safety and efficacy studies.[3] Acetaminophen is the OTC analgesic recommended most by healthcare professionals in the U.S. When used as directed, it is safe and effective, and it is the only OTC pain reliever and fever reducer with professional dosing available for infants under the age of 6 months in the U.S.

Special Populations that Rely on Acetaminophen

For some consumers, including older adults with persistent pain, patients with stomach conditions such as ulcers or other chronic conditions,[4] acetaminophen is often the most appropriate option for pain relief.

In fact, acetaminophen is identified as either a first-line, preferred, or only OTC pain relief option for:

Children under the age of 6 months: Acetaminophen is commonly recommended by pediatricians to relieve pain and reduce fever in children. It is the only OTC pain reliever and fever reducer with professional dosing available for infants under the age of 6 months in the U.S.

Older consumers: Acetaminophen may be a more appropriate choice for older consumers and/or those with underlying medical issues who may be at higher risk for side effects associated with other pain relievers. The American Geriatrics Society (AGS) identifies acetaminophen as the OTC pain reliever of choice for individuals living with persistent pain. For those 60 or older, acetaminophen may be a better clinical choice because it does not carry the risk of stomach bleeding, like other pain relievers might.

Heart disease and/or stroke patients: The American Heart Association (AHA) identifies acetaminophen as a first-line pain relief option for consumers with, or at high risk for, heart disease.

People with high blood pressure: Acetaminophen may be a more appropriate choice of pain reliever for those with high blood pressure as it does not elevate blood pressure like nonsteroidal anti-inflammatory drugs (NSAIDs) can.

Patients with a history of stomach bleeding, stomach ulcers, or heartburn: Acetaminophen may be a more appropriate choice of pain reliever because it does not irritate the stomach.

People with asthma: Acetaminophen may be a more appropriate choice of pain reliever for many people with asthma because it does not make asthma symptoms worse as other pain relievers may.

Patients with kidney disease: The National Kidney Foundation (NKF) identifies acetaminophen as the OTC pain reliever of choice for occasional use in people living with kidney disease.

4 Curfman G. FDA strengthens warning that NSAIDs increase heart attack and stroke risk. Harvard Health Blog. 22 Aug. 2017. Retrieved from: https://www.health.harvard.edu/blog/fda-strengthens-warning-that-nsaids-increase-heart-attack-and-stroke-risk-201507138138.

The Science Behind Acetaminophen

In order to be listed under Prop 65 in California, acetaminophen must be *"clearly shown through scientifically valid testing according to generally accepted principles"* to cause cancer. **The scientific evidence strongly weighs against California identifying acetaminophen as a known carcinogen.** Extensive data generated through epidemiologic, genotoxicity, and animal carcinogenicity studies **do NOT support a conclusion that there is a causal relationship between acetaminophen and cancer.**

- **There is no convincing human data to support carcinogenicity of acetaminophen.**
  Numerous epidemiologic studies have evaluated whether the use of acetaminophen is associated with various types of cancer. For the large majority of cancer types, there is no increased risk with acetaminophen use, even when it is taken for longer periods of time. Although some studies have observed a small increase in risk, these results are considered inconclusive based either on limited data, the inherent limitations of studying humans when one can't control all the relevant variables, or conflicting results from other studies showing no increase in risk.[5]

- **The U.S. Food and Drug Administration (FDA) recent reviews of prescription acetaminophen products did not identify any concerns regarding the human carcinogenicity of acetaminophen.**
  In November 2010, FDA approved a new drug application for a prescription intravenous formulation of acetaminophen with no human carcinogenicity concerns identified. More recently, FDA reviews of new drug applications for acetaminophen combination products (Xartemis XR – approved 2014; Apadaz approved 2018) have not changed their thinking.

- **Animal test results are reassuring and support the safety of acetaminophen.**
  Preclinical studies have shown no meaningful link between acetaminophen exposure and cancer. The International Agency for Research on Cancer (IARC) examined the preclinical study results and their overall evaluation was that acetaminophen is not classifiable as to its carcinogenicity to humans.*[6]

---

5 Weiss NS. Use of acetaminophen in relation to the occurrence of cancer: a review of epidemiologic studies. Cancer Causes Control. 2016;27(12):1411-1418.

*Acetaminophen was classified as Group 3 by IARC (Group 1 – Carcinogenic to humans, Group 2A – Probably carcinogenic to humans, Group 2B – Possibly carcinogenic to humans and Group 3 -Not Classifiable as to its carcinogenicity in humans).

6 International Agency for Research on Cancer (IARC) - Summaries & Evaluations Volume: 73 (1999) (p. 401)

Likely Unintended Consequences of Prop 65 Listing

A significant amount of information is available demonstrating that acetaminophen does not increase the risk of cancer. **Listing acetaminophen under Prop 65 would not only contradict the weight of the scientific evidence, but it would also likely confuse consumers when they decide on pain relief options.** This could lead some sensitive consumers to switch to pain relievers that present greater overall safety concerns for their personal health circumstances. Consumer studies and other research have shown that when access to their preferred dose of acetaminophen is compromised, as many as 40 percent of consumers will switch to an OTC NSAID (aspirin, ibuprofen, or naproxen) without understanding the potential for NSAID-related health risks, including heart attack and stroke.[7,8]

While this research explored compromised access in terms of physical barriers to access (i.e. behind the counter, out of stock), it is reasonable that a Prop 65 warning or listing would serve as a psychological barrier to access for some, thereby pushing consumers to pain medications with a less favorable benefit-risk profile for their individual medical need, to an unproven drug, to non-medical options, or to non-treatment of their pain at all.

In addition, the U.S. Department of Health and Human Services (HHS) identifies acetaminophen as an important alternative to opioids for healthcare professionals to consider. Its draft report entitled *"Draft Report on Pain Management Best Practices: Updates, Gaps, Inconsistencies, and Recommendations"* recommends acetaminophen as a first-line class of medication following standard dosing schedules for non-neuropathic, non-cancer pain, to be utilized with other non-pharmacologic treatments as an alternative to opioids.

7 Alliance For Aging Research, Pain Study Report_Nationwide Survey of U.S. Adults, December 2014. Retrieved from: http://agingresearch.org/CustomPages/view/64

8 Curfman, G. July 13, 2015. FDA strengthens warning that NSAIDs increase heart attack and stroke risk. Harvard Health Publishing. Retrieved from: https://www.health.harvard.edu/blog/fda-strengthens-warning-that-nsaids-increase-heart-attack-and-stroke-risk-201507138138

CHPA® CONSUMER HEALTHCARE PRODUCTS ASSOCIATION

The Consumer Healthcare Products Association (CHPA) is the 138-year-old national trade association representing the leading manufacturers and marketers of over-the-counter (OTC) medicines and dietary supplements. Every dollar spent by consumers on OTC medicines saves the U.S. healthcare system more than $7, contributing a total of $146 billion in savings each year. CHPA is committed to empowering self-care by preserving and expanding choice and availability of consumer healthcare products. For more information, visit chpa.org.

Consumer Healthcare Products Association
1625 Eye Street, NW Suite 600 | Washington, DC 20006 | Phone: (202) 429-9260

MEDICATION SAFETY COMMITTEE
MEETING MINUTES
July 17, 2019 / 10:00 am – 2:00pm

CHA

Members Participating:	**Eddie Avedikian, Candace Fong, Amy Gutierrez, Jeannette Hanni, Randy Kajioka, Kimberly Kirchmeyer, Lori Nolan, Doug O'Brien, Richard Rabens, Diana Schultz, Deepak Sisodiya, Rita Shane, Steve Thompson, Kevin Dorsey Tyler**
Guests:	**Christine Acosta (BoP), Amy Avery (CDPH), Rose McDowell (CDPH), Raj Rajjan (CDPH), Diana Scaturro (OSHPD), Michael Tou**
CHA Staff:	**BJ Bartleson, Alyssa Keefe, Barb Roth**

I. CALL TO ORDER/INTRODUCTIONS (Hanni/Fong)
The committee meeting was called to order by chair Ms. Hanni at 10:05 a.m.

II. MINUTES (Hanni/Fong)
Review of April 3, 2019 meeting minutes.

- ***Update with corrections on page 14 of minutes. Approved with those two corrections.***

III. OLD BUSINESS

A. Sterile Compounding Next Steps (Bartleson)
There are number of hospital pharmacy clean room projects that have not yet started and will not meet the December 2019 deadline. With many hospitals unable to meet the deadline, they must make contingency plans. This may cause delays in patient care. Per the Office of Statewide Health Planning and Development (OSHPD), most hospitals are not aware that this is a complex multi-step process. California Department of Public Health (CDPH) advised that the Central Applications Branch (CAB) application must have a Board of Pharmacy (BoP) license to begin the approval process. CDHP CAB are prioritizing these applications, however they must be complete when submitted. OSHPD and CDPH agreed to meet to identify some common construction problems and errors. Their current consensus is that construction is the problem, not the approval processes (OSHPD, CDPH, and BoP). Engineers and architects do not understand USP 797, not to mention supplier and contractor delays. On June 9, Office of Inspector General (OIG) issued a national recommendation that organizations outsource all non-patient specific compounded drugs (link provided by Ms. Shane and Ms. Keefe).

CHA will issue a message from CHA CEO Carmela Coyle to hospital CEOs, advising them to review their sterile compounding practices in preparation of the December 1, 2019 deadline. The committee agreed that pharmacists need to:

1. Make sure hospital administration is informed and updated.
2. Work on a contingency plan now, if they will not meet the December deadline.
3. Evaluate contractors' knowledge of USP.

- *ACTION: CHA will send link to OIG recommendation to committee members*
- *ACTION: CHA CEO memo will be sent.*

B. USP 800 Hazardous Drugs – Handling in Healthcare Settings (Bartleson/Shane)
Training for handling of USP 800 hazardous drugs must be provided and included in hospital policy. BoP is seeking uniformity with USP with the intent to clarify or include information for patient safety, not to restate the USP in regulations. California Occupational Safety and Health Agency (CalOSHA) involvement regarding workforce is critical.

- *ACTION: Ms. Bartleson to check with Ms. Blanchard-Saiger about CalOSHA involvement.*

C. Inventory Reconciliation and Automatic Dispensing Units (Fong/Bartleson)
There has been concern about some provisions regarding use of Automatic Dispending Units (ADUs) in hospitals and other locations. BoP plans to refine language in the regulations and bring to this committee for review.

- *ACTION: BoP to bring language revisions to committee for review.*

D. Biosimilars (Bartleson/Shane)
Big Pharma is becoming more aggressive in offering rebates, which affects what payers will reimburse for hospital usage. Cedars-Sinai will be reviewing denials and/or patient billing. Sutter does not participate in "white bag issues" (white bagging defined as- when the insurance company insists on a specific drug manufacturer and sends the drug directly to the hospital pharmacy). Committee identified two basic problems:

1. Patient safety – patient specific drug use determined by health plan (payer) getting rebates from pharma rather than physician.
2. White bagging

- *ACTION: BoP to research further.*
- *ACTION: Committee members to send CHA a specific policy addressing this issue, especially if patients are receiving denials. (Ms. Shane and Mr. Sisodiya)*

E. Medication Safety Tool Review (Bartleson)
Medication Safety Tools created by the committee need to be updated or removed from the website. Questions discussed regarding whether the tools are being used; if not being used, and the committee feels they are not relevant, then CHA should remove them from the site.

- *ACTION: CHA to run a web analytics to see if the tools are being viewed.*

IV. NEW BUSINESS

A. SB 1254 Quality Improvement Project (Shane/Stephens)
Ms. Shane is launching a project to develop methodology and has a couple of physicians lined up to review and provide feedback. By end of March, there should be 12 weeks' worth of data. Ms. Shane is gathering questions and will be providing information about the webinar.

- *ACTION: Information only.*

B. CURES Information Exchange Web Service Issues (Bartleson)
The system is integrated, so there is no need to link, which makes reporting much easier. EPIC is working with Department of Justice (DOJ) to get this Memorandum of Understanding (MOU) agreed by all parties. Mr. Avedikian reported that Kaiser has integrated, and it works great. Their MOU is with the health system and the DOJ. Ms. Gutierrez will follow up with their EPIC

pharmacists and get back to Ms. Bartleson. There is an issue with the read receipts.

- *ACTION: Ms. Bartleson and Ms. Kirchmeyer to discuss further.*

C. Labetalol Administration (Stephens)
This is a patient safety issue.

- *Information only.*

IV. LEGISLATION

A. AB 528 – CURES (Bartleson)
The one-day stipulation is difficult. The key is determining when the drug is "dispensed"; when patient picks it up or when the pharmacy prepares it for pick up. The one-day stipulation does not allow for whether the pharmacy sends the information to Atlantic Associates with the "pick up" or "fill" function. There is also concern about the privacy aspect with accurate and exposed information. This is not a problem on the inpatient side. Homeless patients do not have addresses and Atlantic Associates insists on complete information.

- *ACTION: Ms. Bartleson will continue to follow and keep committee members informed*

B. Pharmacy Bills (Bartleson)
Review of Pharmacy bills.

V. STANDING REPORTS

A. Board of Pharmacy (BoP)
1. Two board members, Weisser and Law, have resigned.
2. Board meeting next week in Anaheim.
3. Discussion on implementation on ADDs bill – draft FAQs.

B. California Department of Public Health (CDPH)
Recap of projects.
1. Projects they know about in progress – 91 IV rooms
2. Projects under review or ready to be surveyed - 21
3. Projects completed - 73

C. California Society of Health System Pharmacists (CSHP)
Report included under Pharmacy Bills.

VI. ROUNDTABLE
Add Medication Assisted Treatment to next meeting agenda.

VIII. NEXT MEETING
October 17, 2019 (In Person Meeting –Anaheim)

IX. ADJOURNMENT
Having no further business, the committee adjourned at 1:32 pm.

CHA MEDICATION SAFETY COMMITTEE
2019 ROSTER

Officers

Chair
Candace Fong, Pharm.D
System Director, Pharmacy and Medication Safety
Dignity Health
3400 Data Drive
Rancho Cordova, CA 95670
(916) 851-2678
candace.fong@dignityhealth.org

Chair
Jeanette Hanni, R.Ph, MPA, FCSHP
Bay Area Executive Director of Pharmacy Services
Sutter Health
2350 W. El Camino Real
Mountain View, CA 94040
(650) 934-6967
hannij@sutterhealth.org

Members

Eddie W. Avedikian, PharmD
Pharmacy Operations Manager
Providence Holy Cross Medical Center
2727 Alameda Ave.
Burbank, CA 91505
(818) 847-6327
eddie.avedikian@providence.org

Kathy Ghomeshi, Pharm.D, MBA, BCPS, CPPS
Medication Safety Specialist
UCSF Medical Center
533 Parnassas Avenue
San Francisco, CA 94143
(415) 851-5284
kathy.ghomeshi@ucsf.edu

Amy Gutierrez, PharmD
Vice President, Chief Pharmacy Officer
Kaiser Permanente
12254 Bellflower Boulevard
Downey, CA 90242
(562) 658-3513
Amarylis.C.Gutierrez@kp.org

Nasim Karmali, RPh
Clinical Director, Quality Services
Kaiser Permanente Redwood City Medical Center
1100 Veterans Boulevard
Redwood City, CA 94063-2087
(650) 299-3713
nasim.karmali@kp.org

Lori Nolan-Mullenhour, MSN, RN, NE-BC, CEN
Director, Women & Children's Service Line
Providence Little Company of Mary Medical Center Torrance
4101 Torrance Boulevard
Torrance, CA 90503-4664
(310) 303-6312
lori.mullenhour@providence.org

Doug O'Brien, Pharm.D
Regional Director for Inpatient Pharmacy Services
Kaiser Foundation Hospitals
3240 Arden Way
Sacramento, CA 95825
(510) 301-3990
doug.c.o'brien@nsmtp.kp.org

Richard B. Rabens, MD, MPH, FAAP
Medical Director
Kaiser Permanente
1800 Harrison Street
Oakland, CA 94612
(510) 625-6881
Richard.Rabens@kp.org

Reynaldo Rosario, MSN, RN-BC, CPHQ
Quality Improvement Manager
Santa Clara Valley Medical Center
751 South Bascom Avenue
San Jose, CA 95128-2699
(408) 885-4491
Reynaldo.Rosario@hhs.sccgov.org

Diana Schultz, RPh, MHSA
Sr Specialist, Safe Medication Practices
Sharp HealthCare
8695 Spectrum Center Boulevard
San Diego, CA 92123-1489
(858) 499-6574
diana.schultz@sharp.com

Rita Shane, Pharm.D, FASHP, FCSHP
Chief Pharmacy Officer
Cedars-Sinai Medical Center
8700 Beverly Boulevard
Los Angeles, CA 90048-1865
(310) 423-5611
rita.shane@cshs.org

Deepak Sisodiya, PharmD, MHA
Administrative Director, Pharmacy Services
Stanford Health Care
300 Pasteur Drive
Palo Alto, CA 94305-2200
DSisodiya@stanfordhealthcare.org

Sarah Stephens, Pharm. D, BCPS, CPPS
Medication Safety Coordinator
Kaweah Delta Health Care District
400 W. Mineral King
Visalia, CA 93291
(559) 624-5652
sastephe@kdhcd.org

Kevin Dorsey Tyler, MD, PhD
Medical Director, Clinical Analytics
Enloe Medical Center - Esplanade Campus
1531 Esplanade
Chico, CA 95926-3386
(530) 322-7994
kevin.dorseytyler@enloe.org

Advisory/Ex-Officio

John Christensen, Pharm.D
Pharmaceutical Consultant II
California Department of Public Health
2170 Northpoint Parkway
Santa Rosa, CA 95407
(707) 576-2418
john.christensen@cdph.ca.gov

Loriann DeMartini, Pharm.D
Chief Executive Officer
California Society of Health System Pharmacists
1314 H Street
Sacramento, CA 95814
(916) 447-1033
ldemartini@cshp.org

Randy Kajioka, Pharm.D
Chief of Pharmacy Services
California Correctional Health Care Systems
PO Box 588500
Elk Grove, CA 95758
(916) 379-1677
randy.kajioka@cdcr.ca.gov

Cari Lee, Pharm.D
Pharmaceutical Consultant II
California Department of Public Health
150 North Hill Drive
Brisbane, CA 94005
(415) 330-6779
cari.lee@cdph.ca.gov

Patti Owens
Director of Regulatory Affairs
California Association of Health Facilities
2201 K Street
Sacramento, CA 95816
(916) 432-5201
powens@cahf.org

Anne Sodergren
Assistant Executive Officer
California Board of Pharmacy
1625 N. Market Boulevard
Sacramento, CA 95834
(916) 574-7894
anne.sodergren@dca.ca.gov

Steve Thompson
Director, Pharmacy
California Society of Health System Pharmacists
3330 Lomita Boulevard
Torrance, CA 90505-5073
(310) 517-6997
steven.thompson@tmmc.com

Art Woo, Pharm.D
Pharmaceutical Consultant II
California Department of Public Health
850 Marina Bay Parkway
Richmond, CA 94804-6403
(510) 620-3916
art.woo@cdph.ca.gov

Staff

BJ Bartleson, RN, MS, NEA-BC
Vice President Nursing & Clinical Services
California Hospital Association
1215 K St.
Sacramento, CA 95814
(916) 552-7537
bjbartleson@calhospital.org

Barb Roth
Administrative Assistant
California Hospital Association
1215 K Street, Suite 800
Sacramento, CA 95814
(916) 552-7616
broth@calhospital.org

Medication Safety Committee
Hospital Representation

BY COUNTY

As of July 17, 2019

Denotes number of hospitals/health systems represented within that county.

Contact	Position Type	Represented Organization	County (Represented Org
Candace Fong, Pharm.D	Chair	Dignity Health	San Francisco
Jeanette Hanni, R.Ph, MPA, FCSHP	Chair	Sutter Health	Sacramento
Amy Gutierrez, PharmD	Member	Kaiser Permanente	Alameda
Deepak Sisodiya, PharmD, MHA	Member	Stanford Health Care	Santa Clara
Diana Schultz, RPh, MHSA	Member	Sharp HealthCare	San Diego
Doug O'Brien, Pharm.D	Member	Kaiser Foundation Hospitals	Sacramento
Eddie W. Avedikian, PharmD	Member	Providence Holy Cross Medical Center	Los Angeles
Kathy Ghomeshi, Pharm.D, MBA, BCPS, CPPS	Member	UCSF Medical Center	San Francisco
Kevin Dorsey Tyler, MD, PhD	Member	Enloe Medical Center - Esplanade Campus	Butte
Lori Nolan-Mullenhour, MSN, RN, NE-BC, CEN	Member	Providence Little Company of Mary Medical Center Torrance	Los Angeles
Nasim Karmali, RPh	Member	Kaiser Permanente Redwood City Medical Center	San Mateo
Reynaldo Rosario, MSN, RN-BC, CPHQ	Member	Santa Clara Valley Medical Center	Santa Clara
Richard B. Rabens, MD, MPH, FAAP	Member	Kaiser Permanente	Alameda
Rita Shane, Pharm.D, FASHP, FCSHP	Member	Cedars-Sinai Medical Center	Los Angeles
Sarah Stephens, Pharm. D, BCPS, CPPS	Member	Kaweah Delta Health Care District	Tulare
Anne Sodergren	Ex-officio	California Board of Pharmacy	
Art Woo, Pharm.D	Ex-officio	California Department of Public Health	
Cari Lee, Pharm.D	Ex-officio	California Department of Public Health	
John Christensen, Pharm.D	Ex-officio	California Department of Public Health	
Loriann DeMartini, Pharm.D	Ex-officio	California Society of Health System Pharmacists	
Patti Owens	Ex-officio	California Association of Health Facilities	
Randy Kajioka, Pharm.D	Ex-officio	California Correctional Health Care Systems	
Steve Thompson	Ex-officio	California Society of Health System Pharmacists	

GUIDELINES FOR THE
CALIFORNIA HOSPITAL ASSOCIATION
MEDICATION SAFETY COMMITTEE

I. NAME

The name of this committee shall be the Medication Safety Committee.

II. MISSION

The mission of the Medication Safety Committee is to provide leadership within the health care community to promote the highest standards related to the safe and effective use of medications.

III. PURPOSE

The purpose of the Medication Safety Committee is to provide a forum for diverse multi-disciplinary health care organizations, which includes health care delivery organizations, patient safety organizations, discipline specific professional associations/organizations and regulatory agencies, to promote safe medication practices in the state of California. The Committee will focus on acting as a source of medication safety expertise, providing a venue for the coordination of medication safety activities and making recommendations related to medication safety legislation and regulations.

IV. COMMITTEE

The Committee (the "Committee") shall consist of a minimum of 16 representatives and not more than 35 representatives from hospital members and the following related organizations:

California Department of Public Health California
Society of Health System Pharmacists California
Board of Pharmacy
Centers for Medi-Care and Medi-Caid Services
Collaborative Alliance for Nursing Outcomes
Association of California Nurse Leaders California
Medical Association
California HQI and CHPSO
Risk Management Association
Representatives from the following CHA committees/centers:
Center for Behavioral Health
- Rural Health Center
- Quality Committee
- Joint Committee on Accreditation and Licensing Center
- for Hospital Medical Executives EMS/Trauma
- Committee
- Hospital Based Clinics Committee
- Center for Post Acute Care
- Governance

A. MEMBERSHIP

1. Membership on the Committee shall be based upon membership in CHA, or organizations that have a direct relationship to the purpose and mission of the Committee. CHA members will be hospital members. Non-hospital members are ex-officio members and can only be appointed to the Committee at the discretion of the CHA staff liaison.
2. The CHA Committee members shall consist of various representatives from large hospital systems, public institutions, private facilities, free-standing facilities, small and rural facilities, university/teaching facilities and specialty facilities. A member may fulfill more than one required membership position.
3. Hospital members are appointed by CHA Staff per recommendation of hospital Committee members and per hospital and non-hospital membership requirements listed above.
4. Guidelines for membership – these guidelines should be used when selecting potential new members for the Committee:
   a) Demonstrated experience in medication safety and understanding of regulatory environment based on current or recent job responsibilities
   b) Contributions to medication safety at the organizational and/or professional level
   c) Practice experience related to medication safety and regulatory compliance: at least 3 years (preferred).
5. Term:
   a) Terms of office shall be based on member participation and desire to remain active on the Committee. The CHA staff liaison will perform an annual review of member attendance, participation and desire to remain active on the committee.
   b) Chairs and Co-Chair positions will be filled by hospital members only and selected by the CHA staff liaison per recommendation of the present chair, co-chairs and by other members of the Committee. They will be selected based on their leadership and desire to fill the position.

B. MEMBER RESPONSIBILITIES

1. Provide hospital-industry leadership to the Committee and CHA Board of Trustees.
2. Identify issues and develop possible solutions and best practices to improve the safety of the medication use process.
3. Work cooperatively with key stakeholders to develop creative solutions.
4. Provide communication to member hospitals regarding medication safety issues.
5. Maintain/increased awareness of the legislative and regulatory environment with regard to medication safety issues.

C. COMMITTEE MEETINGS

1. Meetings of the Committee shall be held quarterly in person.
2. To maintain continuity, substitution of members should be discussed with the staff liaison and co-chairs on an individual basis.
3. Three consecutive unexcused absences by a Committee member will initiate a review by the co-chairs and CHA staff liaison for determination of the Committee member's continued service on the Committee.
4. Special meetings may be scheduled by the co-chair, majority vote, or CHA staff liaison.

D. VOTING

1. Voting rights shall be limited to members of the Committee, and each member present shall have one vote. Voting by proxy is not acceptable.
2. All matters requiring a vote of the Committee must be passed by a majority of a quorum of the Committee members present at a duly called meeting or telephone conference call.

E. QUORUM

Except as set forth herein, a quorum shall consist of a majority of members present or not less than eight.

F. MINUTES

Minutes of the Committee shall be recorded at each meeting, disseminated to the membership, and approved as disseminated or as corrected at the next meeting of the Committee.

V. OFFICERS

The officers of the Committee shall be the Committee chair, co-chair and CHA staff liaison.

A. SUB-COMMITTEES

1. Task forces of the Committee may be formed at the discretion of the Committee chairs and members and CHA staff liaison for the purpose of conducting activities specific to a special topic or goal.

VI. GENERAL PROVISIONS

Goals, and objectives, shall be developed annually by the Committee with approval by the CHA staff liaison. Quarterly updates and progress reports shall be completed by the Committee and CHA staff.

Staff leadership at the state level shall be provided by CHA with local staff leadership provided by Hospital Council, the Hospital Association of Southern California, and the Hospital Association of San Diego and Imperial Counties. The primary office and public policy development and advocacy staff of the Committee shall be located within the CHA office.

The Committee staff liaison shall be an employee of CHA.

VII. AMENDMENTS

These Guidelines may be amended by a majority vote of the members of the Committee at any regular meeting of the Committee and with approval by CHA.

VIII. LEGAL LIMITATIONS

Any portion of these Guidelines which may be in conflict with any state or federal statute or regulations shall be declared null and void as of the date of such determination.

Information provided in meetings is not to be sold or misused.

IX. CONFIDENTIALITY FOR MEMBERS

Many items discussed are confidential in nature, and confidentiality must be maintained. All Committee communications are considered privileged and confidential, except as noted.

X. CONFLICT OF INTEREST

Any member of the Committee who shall address the Committee in other than a volunteer relationship excluding CHA staff and who shall engage with the Committee in a business activity of any nature, as a result of which such party shall profit either directly or indirectly, shall fully disclose any such financial benefit expected to CHA staff for approval prior to contracting with the Committee and shall further refrain, if a member of the Committee, from any vote in which such issue is involved.