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MODEL STANDARDS FOR PHARMACY COMPOUNDING OF NON-HAZARDOUS STERILE PREPARATIONS



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Association nationale des organismes de réglementation de la pharmacie

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Model Standards for Pharmacy Compounding of Non-hazardous Sterile Preparations

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1. INTRODUCTION

The compounding of sterile preparations requires high-quality standards to ensure preparation quality and safety. Parenteral therapies are becoming more complex, and patients may now receive continuous antibiotic therapy or chemotherapy, among other therapies, for several days at home. Consequently, greater attention must be paid to the environment in which these preparations are prepared, the training of personnel and quality assurance procedures to prevent complications and protect the public more generally.

Evolving practice and increased awareness of the inherent dangers of compounding sterile preparations for the health of both patients and compounding personnel^{1,2,3,4} led to the need to review the “Guidelines to Pharmacy Compounding” published by the National Association of Pharmacy Regulatory Authorities (NAPRA) in October 2006.

The new NAPRA Model Standards for Pharmacy Compounding of Non-hazardous Sterile Preparations have been adapted from standards originally developed by the Ordre des pharmaciens du Québec, which are in turn based on General Chapter <797> of the United States Pharmacopeia – National Formulary (USP–NF) in effect in the United States since 2004. Their preparation was led by the NAPRA ad hoc Committee on Pharmacy Compounding and involved extensive consultation with experts and stakeholders.

1 Bussi eres JF, Prot S. Perspectives sur les pr eparations magistrales en pharmacie au Qu ebec. *Pharmactuel*. 2004;37(3):File 1.

2 Selenic D, Dodson DR, Jensen B, Arduino MJ, Panlilio A, Archibald LK. *Enterobacter cloacae* bloodstream infections in pediatric patients traced to a hospital pharmacy. *Am J Health Syst Pharm*. 2003;60(14):1440-6.

3 Patel PR, Larson AK, Castel AD, Ganova-Raeva LM, Myers RA, Roup BJ, et al. Hepatitis C virus infections from a contaminated radiopharmaceutical used in myocardial perfusion studies. *JAMA*. 2006;296(16):2005-11.

4 Kastango ES. The cost of quality in pharmacy. *Int J Pharm Compound*. 2002;6(6):404-7.



2. OBJECTIVES

The aim of these Model Standards is to provide pharmacists and pharmacy technicians who compound non-hazardous sterile preparations with the standards necessary to evaluate their practice, develop service-related procedures and implement appropriate quality controls for both patients and compounding personnel, with a view to guaranteeing the overall quality and safety of sterile preparations. The Model Standards will come into effect in each province/territory once they have been adopted by the respective provincial/territorial pharmacy regulatory authorities.

These Model Standards represent the minimum requirements to be applied in compounding sterile preparations; however, it is always possible to exceed these standards. The use of other technologies, techniques, materials and procedures may be acceptable, so long as they are proven to be equivalent or superior to those described here.

These Model Standards support NAPRA's Model Standards of Practice for Canadian Pharmacists and Pharmacy Technicians^{5,6}, as well as other policies and guidelines that may be in place in provincial/territorial jurisdictions.

5 National Association of Pharmacy Regulatory Authorities (NAPRA). *Model standards of practice for Canadian pharmacists*. Ottawa, ON: NAPRA; 2009. Available from: http://napra.ca/Content_Files/Files/Model_Standards_of_Prac_for_Cdn_Pharm_March09_Final_b.pdf

6 National Association of Pharmacy Regulatory Authorities (NAPRA). *Model standards of practice for Canadian pharmacy technicians*. Ottawa, ON: NAPRA; 2011. Available from: <http://napra.ca/pages/PharmacyTechnicians/pharmacytechniciansstandards.aspx>



3. REGULATORY FRAMEWORK

Compounded sterile preparations are prepared by many health care professionals, including nurses, physicians, pharmacists and pharmacy technicians. However, the majority of sterile compounding is performed by pharmacy personnel under the supervision of pharmacists. Although these standards could serve as best practices for other health care practitioners, they pertain specifically to pharmacists, pharmacy technicians and pharmacies where compounded sterile preparations are prepared.

The preparation of medications (pharmacy compounding) has always been an integral part of the practice of pharmacy. It is essential to the delivery of health care and allows for personalized therapeutic solutions to improve patient care. However, pharmacy compounding must always be carried out within a prescriber–patient–pharmacist relationship. Provincial/territorial pharmacy regulatory authorities are responsible for regulating a pharmacy’s compounding services in these situations.

In situations involving requests to compound preparations outside of a prescriber–patient–pharmacist relationship, in the absence of a patient-specific prescription, the preparation activities fall under the federal legislative framework. For example, the bulk preparation of compounded preparations in the absence of a prescriber–patient–pharmacist relationship would fall under the federal legislative framework.

Health Canada is the federal department responsible for the *Food and Drugs Act* and the *Controlled Drugs and Substances Act* and their associated regulations. In January 2009, Health Canada developed its “Policy on Manufacturing and Compounding Drug Products in Canada”⁷. At the time these Model Standards were prepared, Health Canada was examining this policy with a view to creating new standards for situations not covered within the practice of pharmacy or under the current federal licensing framework, such as commercial compounding manufacturing.

NAPRA’s professional competencies for Canadian pharmacists and pharmacy technicians at entry to practice provide guidance for developing an ethical, legal and professional practice. One of these competencies specifies that a pharmacist or pharmacy technician must seek guidance when uncertain about his or her own knowledge, skills, abilities or scope of practice. Therefore, individuals who do not have the knowledge, training, expertise, facilities or equipment required to compound sterile products must refer patients to a colleague who does have the competencies and facilities required to do so or, where permitted by provincial/territorial legislation, ask another pharmacy to compound the product for them.

Compounded sterile preparations include the following types of medications:

- nasal inhalation solutions
- respiratory therapy solutions
- solutions for live organ and tissue or graft baths
- injections (e.g., intramuscular, intravenous, intrathecal, intradermal, subcutaneous)
- irrigation solutions for wounds and body cavities (e.g., thoracic, spinal, abdominal, pelvic)
- ophthalmic drops and ointments
- otic drops for intratympanic administration
- parenteral nutrition
- dialysis solutions

7 Health Canada, Health Products and Food Branch Inspectorate. *Policy on manufacturing and compounding drug products in Canada*. POL-051. Ottawa, ON: Health Canada; 2009. Available from: http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/pol_0051-eng.php



- allergen extracts
- topical preparations (where sterility is essential to the therapy, e.g., for patients with burns)
- radiopharmaceuticals

Pursuant to these Model Standards, sterility is also required for the reconstitution and certain manipulations (according to manufacturers' instructions) of sterile products approved by Health Canada and for the repackaging of approved sterile products, regardless of the route of administration.



4. ABBREVIATIONS

The following abbreviations are used in this document.

| Abbreviation | Definition |
|--------------|--|
| ABHR | Alcohol-based hand rub |
| ACD | Automated compounding device |
| ACPH | Air changes per hour |
| BUD | Beyond-use date |
| CAI | Compounding aseptic isolator |
| CETA | Controlled Environment Testing Association |
| CFU | Colony-forming unit |
| GFS | Gloved fingertip sampling |
| HEPA | High-efficiency particulate air |
| HVAC | Heating, ventilation and air conditioning |
| ISO | International Organization for Standardization |
| LAFW | Laminar airflow workbench |
| NF | National Formulary (United States) |
| PEC | Primary engineering control |
| PPE | Personal protective equipment |
| USP | United States Pharmacopeia |



5. CORE REQUIREMENTS FOR A STERILE COMPOUNDING SERVICE

5.1 Personnel

5.1.1 Roles and responsibilities

5.1.1.1 Pharmacy manager⁸ or pharmacy department head⁹

The pharmacy manager or pharmacy department head is responsible for developing, organizing and supervising all activities related to pharmacy compounding of sterile preparations. This person may share or assign these responsibilities to a pharmacist or pharmacy technician, who will be designated as the sterile compounding supervisor. If the designated pharmacist or pharmacy technician chooses not to perform these activities, the pharmacy manager or pharmacy department head must assume the responsibilities of the sterile compounding supervisor and must therefore be qualified to perform compounding of non-hazardous sterile preparations in the pharmacy.

If these responsibilities are assigned to a pharmacist or pharmacy technician, the pharmacy manager or pharmacy department head must ensure that the sterile compounding supervisor fulfills them adequately.

5.1.1.2 Sterile compounding supervisor

Definition

A pharmacist or pharmacy technician designated to supervise activities related to the compounding of non-hazardous sterile preparations. This person works with the pharmacy manager or pharmacy department head and with the compounding personnel.

The sterile compounding supervisor develops, organizes and oversees all activities related to sterile-preparation compounding. These responsibilities are assigned by the pharmacy manager or pharmacy department head.

In accordance with the appropriate supervision protocol and appropriate quality control measures, the sterile compounding supervisor may assign technical tasks related to sterile-preparation compounding to a pharmacy assistant with the appropriate training, using a formal delegation process that complies with the requirements of the provincial/territorial authority.

Responsibilities

The sterile compounding supervisor ensures that the following requirements are met:

- A personnel training and assessment program is implemented.
- Personnel know and fully comply with policies and procedures.
- Appropriate measures are taken to ensure the safety of personnel during each preparation.
- Policies and procedures covering all activities are developed, regularly reviewed, updated (at least every 3 years or more frequently when standards have changed) and always followed (*see Appendix 1*).

⁸ In the context of this document, a pharmacy manager in the province of Québec is the pharmacist who owns the pharmacy; in other Canadian jurisdictions, a pharmacy manager is the pharmacist designated as the manager by the pharmacy owner and/or recognized as the manager by the provincial/territorial authority.

⁹ In the context of this document, the pharmacy department head must be a pharmacist licensed to practise pharmacy by the relevant provincial/territorial pharmacy regulatory authority.

- The facilities and equipment used to compound sterile preparations meet requirements and are maintained, calibrated or certified according to manufacturers' specifications or standards, whichever are more stringent.
- The existing compounding process yields high-quality sterile preparations that are safe for patients.
- The available, recognized scientific literature is used to determine stability and to establish the beyond-use date (BUD) for each sterile preparation.
- A quality assurance program, designed to ensure that preparation activities are performed in accordance with standards of practice, scientific standards, existing data and relevant information, is implemented and followed.
- Current editions of mandatory and supplementary references are available and updated regularly. Appendix 2 lists required publications and suggestions for supplementary references.
- All records required by the Model Standards are completed, maintained and readily available for audit and inspection purposes.

5.1.1.3 Compounding personnel

Definition

a) A pharmacist or pharmacy technician who prepares or supervises the compounding of sterile preparations

- for patients of the facility or pharmacy where the pharmacist or pharmacy technician is employed;

OR

- where permitted by provincial/territorial legislation, for patients of another facility or pharmacy upon request.

When more than one pharmacist or pharmacy technician is involved in dispensing a compounded sterile preparation, whether working in the same or different facilities/pharmacies, responsibilities toward the patient are shared between them. In such instances, all parties must comply with provincial/territorial requirements and standards regarding inter- and intra-professional collaboration.

b) A pharmacy assistant with appropriate training¹⁰, who prepares sterile preparations or performs other technical tasks related to sterile compounding only when assigned to do so by the sterile compounding supervisor and only after completion of a formal delegation of duties from a pharmacist to the pharmacy assistant, in compliance with the requirements of the provincial/territorial authority.

Responsibilities

The compounding pharmacist or pharmacy technician must

- perform or supervise compounding activities;
- ensure compliance with policies and procedures related to the compounding of non-hazardous sterile preparations;
- enforce or ensure compliance with required rules relating to asepsis, hygiene, cleanliness and safety;

¹⁰ Please consult the relevant provincial/territorial pharmacy regulatory authority for training requirements defined in each jurisdiction.



- ensure that all records related to ongoing activities are completed and initialled;
- ensure that all data required for monitoring and reproducing the preparation are recorded;
- ensure that the equipment, instruments and space used are properly cleaned and maintained;
- ensure application of and compliance with existing compounding procedures;
- ensure that there is a compounding procedure/worksheet for each preparation produced;
- ensure the accuracy of calculations and measurements;
- ensure that appropriate equipment and instruments are used for each preparation to be produced;
- follow the compounding process defined in the compounding protocol;
- perform verification during the various stages of compounding and verify the final preparation;
- ensure that all required verification and quality control measures are performed to ensure the quality and sterility of each preparation;
- ensure that preparations are packaged and labelled in accordance with provincial/territorial requirements and that a BUD is included on the label (*see* section 6.1);
- when a sterile preparation is prepared on behalf of another facility/pharmacy (where permitted by provincial/territorial legislation), provide, orally and in writing, any information required for storing and transporting such medications (storage method, precautions, suggested BUD, etc.) to the pharmacist or pharmacy technician at the facility/pharmacy where the preparation will be dispensed;
- ensure that the final preparation is properly stored until delivery to the patient or to the pharmacist who ordered it (where compounding is undertaken by another pharmacy, as permitted by provincial/territorial legislation);
- when a preparation must be recalled, notify the pharmacist or pharmacy technician at any pharmacy/facility where the product was dispensed;
- before dispensing or releasing a preparation to the patient, ensure that all standards of practice associated with dispensing the preparation have been met, including an assessment of therapeutic appropriateness, patient consultation and education, documentation and other patient care activities;
- when a sterile preparation has been prepared on behalf of another facility/pharmacy (where permitted by provincial/territorial legislation), ensure that effective communication and collaboration occur between the pharmacists and pharmacy technicians at both facilities to clarify who is responsible for which aspects of patient care and to ensure continuity of care¹¹.

The responsibilities of a pharmacy assistant assigned to prepare sterile preparations or perform other technical tasks related to sterile compounding are determined at the discretion of the sterile compounding supervisor. The sterile compounding supervisor should assign only those tasks permitted by provincial/territorial legislation and for which the pharmacy assistant has the appropriate training¹². The sterile compounding supervisor must ensure that the pharmacy assistant is supervised by a pharmacist or pharmacy technician according to established supervision protocols and appropriate quality measures.

11 National Association of Pharmacy Regulatory Authorities (NAPRA). *Model standards of practice for Canadian pharmacists*. Ottawa, ON: NAPRA; 2009. Available from: http://napra.ca/Content_Files/Files/Model_Standards_of_Prac_for_Cdn_Pharm_March09_Final_b.pdf

12 Please consult the relevant provincial/territorial pharmacy regulatory authority for training requirements defined in each jurisdiction.



5.1.2 Training and assessment

Compounding personnel and cleaning and disinfecting personnel have a major impact on the risks associated with contamination of preparations. Stringent work methods^{13,14} are therefore required.

Integration and maintenance of required competencies is achievable only with adequate training and assessment.

5.1.2.1 Conditions

Pharmacists and pharmacy technicians involved in the organization, training, compounding, supervision or quality control of sterile-product preparations must have the appropriate mix of education and experience. In the case of the sterile compounding supervisor, the person must also possess previous work experience supervising activities of a similar nature.

All new personnel involved in compounding sterile preparations must successfully complete a workplace training and competency assessment program pertinent to the type of preparations to be produced.

Compliance with operating procedures and use of appropriate techniques for compounding sterile preparations must be evaluated as part of the competency assessment program for personnel involved in compounding sterile preparations.

The assessment results and any corrective measures imposed must be recorded, and these records must be retained as per provincial/territorial requirements.

The sterile compounding supervisor must ensure that all compounding personnel have the knowledge and skills required to perform quality work.

5.1.2.2 Initial training and assessment program

Compounding personnel

The initial training and assessment program for compounding personnel must have the following components:

- reading and understanding the policies and procedures related to compounded sterile preparations (*see* Appendix 1);
- theoretical training, with assessment covering various topics, including those listed in Appendix 3;
- individualized practical training and assessment in the workplace clean room (*see* section 7 and Appendix 3);
- assessment of aseptic techniques, based on gloved fingertip sampling (GFS) and a media fill test, for the various types of sterile preparations to be compounded.

Personnel must pass GFS and a media fill test before working in the compounding area for non-hazardous sterile products.

Any compounding employee who has successfully completed the initial workplace training and assessment program may begin work in the compounding of sterile preparations. Employees with limited experience may require additional training and supervision.

13 Thomas M, Sanborn M, Couldry R. I.V. admixture contamination rates: traditional practice site versus a class 1000 cleanroom. *Am J Health Syst Pharm.* 2005;62(22):2386-92.

14 Trissel LA, Gentempo JA, Saenz LM, Woodard MY, Angeles CH. Effect of two work practice changes on the microbial contamination rates of pharmacy-compounded sterile preparations. *Am J Health Syst Pharm.* 2007;64(8):837-41.



Cleaning and disinfecting personnel

The initial training and assessment program for cleaning and disinfecting personnel must have the following components:

- theoretical training and assessment covering the issues and particularities of cleaning and disinfecting the premises and equipment (*see* Appendix 3 for a list of the elements to cover as part of the theoretical assessment of cleaning and disinfecting personnel);
- practical training and assessment in the areas reserved for compounding sterile preparations.

Any cleaning and disinfecting employee who has successfully completed theoretical and practical training in the workplace may perform cleaning duties in the sterile-preparation compounding facilities, in accordance with established procedures.

The sterile compounding supervisor must ensure appropriate training of all new cleaning and disinfecting personnel.

In health care facilities, the sterile compounding supervisor must work closely with the head of environmental services and the head of infection prevention and control to develop joint work and training procedures, which must be understood and followed by all cleaning and disinfecting personnel.

Other persons

Any other person (whether an employee or not) who enters the sterile compounding area or who is involved in sterile compounding processes must be adequately trained and must follow and comply with specific policies and procedures. This requirement covers contractors, volunteers and employees, whether they are students, interns, equipment maintenance personnel or any other type of personnel.

5.1.2.3 Competency assessment program

Sterile compounding supervisor

Qualifications

- The sterile compounding supervisor must have successfully completed training (i.e., courses) in the compounding of sterile preparations, maintained up-to-date knowledge and demonstrated the required competencies.
- The sterile compounding supervisor must also have the competency required to manage a safe, high-quality sterile-preparation compounding area.

Frequency of assessment

- The sterile compounding supervisor must be evaluated for knowledge and abilities, at the same frequency as compounding personnel, by a third party (an evaluator with expertise in sterile-preparation compounding, at arm's length from the facility/pharmacy and free of any real or perceived conflict with the individual being evaluated).
- The third-party evaluator (either a pharmacist or pharmacy technician) must meet the criteria set out in section 5.1.2.4 for third-party evaluators.



Compounding personnel

Content of assessment

A competency assessment program for all compounding personnel (pharmacists, pharmacy technicians and pharmacy assistants) must be implemented in the workplace. This program must include the following:

- a theoretical test measuring required knowledge of policies and procedures and the aseptic compounding process (*see Appendix 3*);
- a practical test in the workplace clean room (including GFS and a media fill test) to evaluate compliance with operating procedures and knowledge of aseptic compounding processes.

Frequency of assessment

All personnel (pharmacists, pharmacy technicians and pharmacy assistants) assigned to the compounding of sterile preparations must undergo assessment at the following frequencies:

- at least once a year in the workplace for preparations with low or medium risk level;
- at least twice a year in the workplace for preparations with high risk level.

An explanation of low-, medium- and high-risk preparations can be found in section 6.1.3.

The results of these assessments should be noted in each employee's file and must be retained for the period specified by the relevant provincial/territorial regulatory authority.

Cleaning and disinfecting personnel

Content of assessment

A competency assessment program for cleaning and disinfecting personnel must be implemented in the workplace (*see Appendix 3* for a list of elements to be covered during training).

Frequency of assessment

All cleaning and disinfecting personnel must be evaluated at least once a year in the workplace.

The results of these assessments should be noted in each employee's file and must be retained for the period specified by the relevant provincial/territorial regulatory authority.

Failures (all personnel)

Compounding personnel who fail the written or practical assessment must immediately stop sterile compounding and redo their training. Cleaning and disinfecting personnel who fail the practical assessment must immediately stop cleaning and disinfecting and redo their training. An individual may resume assigned duties after passing the elements previously failed.

In case of repeated failures, a decision must be made regarding permanent termination of sterile-preparation compounding or cleaning and disinfecting activities.

Pharmacist who never compounds sterile preparations but whose role includes supervising pharmacy technicians and pharmacy assistants

A pharmacist whose activities are limited to supervising a pharmacy technician or pharmacy assistant during sterile-preparation compounding



- may be exempted from the practical section of the assessment of competency in aseptic compounding, the media fill test and GFS;
- must possess a good understanding of the policies and procedures related to sterile compounding and demonstrated ability to determine whether the pharmacy technicians and pharmacy assistants are complying with aseptic processes, in order to quickly detect any risk of error and possible contamination;
- must pass the practical section of the training program regarding assessment of the aseptic compounding process, the media fill test and GFS, if there is a possibility that this pharmacist will compound sterile preparations on an occasional basis.

Pharmacist on duty in a health care facility

Any pharmacist on duty in a health care facility where a pharmacist will be expected to compound sterile preparations must receive the same training as a compounding pharmacist and must undergo annual assessment of competency in sterile-preparation compounding.

5.1.2.4 Management of the competency assessment program

Sterile compounding supervisor and delegation of employee training

The sterile compounding supervisor is responsible for the training of and competency assessment program for all employees involved in compounding sterile preparations. The supervisor may

- assign the training portion of the program to a pharmacist or pharmacy technician on the supervisor's team, while continuing to perform the assessment portion;

OR

- assign both training and assessment of personnel to a third-party evaluator.

Third-party evaluator

If the sterile compounding supervisor assigns the training and assessment of compounding personnel and cleaning and disinfecting personnel to a third party,

- the third party must be a pharmacist or pharmacy technician with expertise in compounding sterile preparations;
- the third party must be at arm's length from the pharmacy or facility (independence);
- the third party must be free of any real or perceived conflict of interest with the individual being evaluated;
- the sterile compounding supervisor must ensure that the third-party evaluator is qualified to fulfill the mandate;
- the third-party evaluator must have training that covers the compounding of sterile preparations and certification that his or her competencies in this area are being maintained and developed;
- the third-party evaluator's annual competency assessment must include the same elements as those of a competency assessment program for compounding personnel, as described in section 5.1.2.3 above.

The third-party evaluator may perform training and competency assessment at the workplace or at an alternate location. Regardless of the location where the training and assessment are performed, the third-party evaluator must evaluate specific policies and procedures in effect in the workplace.



5.2 Policies and procedures^{15, 16}

The quality, efficacy and absence of contamination of the final preparation depend upon, among other things, full compliance with compounding procedures.

- The sterile compounding supervisor must establish the content of policies and procedures, providing detailed descriptions of all activities in the pharmacy's compounding of non-hazardous sterile preparations (*see* Appendix 1). The supervisor must also ensure application of and compliance with these policies and procedures.
- Procedures must be clear, must follow a standard format and must include an index for easy access to information when it is needed. Appendix 4 may be used as a model for developing these procedures.
- The sterile compounding supervisor must ensure that all established policies and procedures are promptly updated whenever there is a change in practice or in standards. In addition, policies and procedures must be reviewed at least every 3 years.
- The drafting and revision dates, the date of each change and the names of authors and reviewers must be included in each policy or procedure.
- Where compounding is undertaken by another pharmacy, as permitted by provincial/territorial legislation, the pharmacist or pharmacy technician at the dispensing facility should include in its general procedures manual information about policies and procedures for acquiring compounded sterile preparations for patients (originating pharmacy, entry in the file, delivery, etc.).

5.3 Facilities and equipment

In addition to the conduct and competency of personnel, facility design (spaces, ventilation, materials, etc.) helps in achieving the objectives of these Model Standards.

Sterile-preparation compounding facilities must be designed and built in accordance with these Model Standards, with provincial/territorial and local regulations and, for health system facilities, with other applicable standards regulating the construction of buildings.

5.3.1 ISO Standard 14644-1

ISO Standard 14644-1 includes a classification of air cleanliness requirements for facilities and clean rooms (*see* Table 1), specifying the allowable concentration of airborne particles for each class. To achieve and maintain a particular ISO class for a clean room, all particle-generating sources must be controlled.

15 United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013. pp. 44, 47, 54, 55.

16 Pharmacy Compounding Accreditation Board (PCAB). Standard 1.40: Standard operating procedures compliance indicators. In: *PCAB accreditation manual*. Washington, DC: PCAB; 2011. p. 7.



Table 1

| Classes of air cleanliness for airborne particulates in clean rooms and clean areas, according to ISO 14644-1 | |
|---|--|
| ISO Class | Maximum concentration of non-viable particles $\geq 0.5 \mu\text{m}$ diameter, measured under dynamic operating conditions (particles per m^3 of air) |
| 3 | 35.2 |
| 4 | 352 |
| 5 | 3 520 |
| 6 | 35 200 |
| 7 | 352 000 |
| 8 | 3 520 000 |

ISO = International Organization for Standardization; μm = micrometre; m^3 = cubic metre.

5.3.2 Facilities reserved for the compounding of non-hazardous sterile preparations

The requirements for facilities vary, depending on whether the sterile preparations to be compounded are non-hazardous or hazardous, although several of these requirements are similar for the two types of products. This section describes only the requirements for facilities involved in the compounding of non-hazardous sterile preparations. Users should consult the companion document, “Model Standards for Pharmacy Compounding of Hazardous Sterile Preparations,” for requirements pertaining to the compounding of hazardous preparations.

5.3.2.1 Dimensions

Areas reserved for the compounding of non-hazardous sterile preparations must be large enough to

- facilitate compounding;
- allow cleaning and disinfecting without constraint;
- ensure good flow of people, equipment and materials.

5.3.2.2 Lighting

The lighting must be sufficient and fixtures located so as to

- facilitate the sterile compounding process;
- allow verification at all stages of compounding.

5.3.2.3 Heating, ventilation and air conditioning system for controlled rooms (clean room and anteroom)

The air in controlled rooms must be “clean,” and levels of airborne particulates must be controlled. Thus, the facility’s heating, ventilation and air conditioning (HVAC) system must be designed to minimize the risk of airborne contamination in controlled rooms. It must also be designed to achieve and maintain the appropriate ISO class for clean rooms¹⁷ and anterooms (see section 5.3.2.5, Table 2 and Table 3).

The air supplied to areas used for compounding non-hazardous sterile preparations must pass through a high-efficiency particulate air (HEPA) filter to ensure a very high level of cleanliness. The intake air must come from the ceiling via diffusers, each fitted with a terminal HEPA filter¹⁸.

17 United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013. pp. 372-4.

18 Health Canada, Health Products and Food Branch Inspectorate. *Good manufacturing practices (GMP) guidelines – 2009 edition, Version 2*. GUI-0001. Ottawa, ON: Health Canada; 2009, revised 2011 Mar 4. p. 85. Available from: <http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui-0001-eng.php>



All sources that generate particles must be controlled to achieve and maintain the ISO class for clean rooms and anterooms used to compound non-hazardous sterile preparations¹⁹.

The air quality in controlled rooms must comply with ISO 14644-1, according to the specifications listed in Table 1, under dynamic operating conditions, as follows: the number of particles $\geq 0.5 \mu\text{m}$ diameter per cubic metre of air must be verified while compounding personnel perform or simulate a typical sterile-product preparation (e.g., media fill).

The particle count must be performed by trained, qualified personnel at least every 6 months as part of an internal quality control program for facilities and the primary engineering control (PEC). The particle count may also be measured by a qualified certifier (*see* Appendices 5 and 6).

Return air intakes should be installed at the bottom of walls²⁰, forcing the particles to flow downward. In older facilities, an airflow analysis must be performed under dynamic operating conditions (using the air speed achieved at the front of the PEC) to ensure that the location of the return air intakes does not hinder the compounding process.

An air conditioning system must be included in the HVAC system to help ensure the comfort of personnel wearing personal protective equipment (PPE).

5.3.2.4 Windows and openings

Controlled rooms must not have windows or doors opening directly to the exterior of the building. If any windows are present, they must be sealed. If any doors lead to the outside or to a non-controlled area (other than the doors designated for accessing the room), they must be sealed. An environmental control procedure and a housekeeping procedure, including the cleaning of sealed windows and doors, must be implemented by cleaning and disinfecting personnel.

5.3.2.5 Compounding areas

Compounding areas must have at least two separate controlled rooms, enclosed and physically separated by a wall: a clean room, where the PEC (e.g., laminar airflow workbench [LAFW], compounding aseptic isolator [CAI]) is located, and an anteroom, located next to the clean room.

For low- and medium-risk compounding (*see* section 6.1.3 for an explanation of low-, medium- and high-risk compounding), it is acceptable to build a compounding area consisting of an ante-area and a clean area with no wall separating the two areas. In the absence of a wall between the ante-area and the clean area, there must be displacement airflow with a velocity of at least 40 feet per minute (12.2 metres per minute) from the clean area to the ante-area. This principle of displacement airflow shall not be applied for high-risk compounding. The following sections of the Model Standards assume a facility design with a clean room and an anteroom separated by a wall. Where a pharmacy has built a sterile compounding area with a displacement airflow of at least 40 feet per minute (12.2 metres per minute) from the clean area to the ante-area, the terms “clean room” and “anteroom” in these sections should be read as “clean area” and “ante-area.”

Clean room

The clean room is a room in which atmospheric properties (temperature, content of particles and microorganisms, air pressure, airflow, etc.) are controlled. The functional parameters of the clean room are maintained at a specific level (*see* Table 2). The room is designed to minimize the introduction, generation and retention of particles.

19 United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013. pp. 372-4.

20 United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013. p. 373.



The clean room must be physically separated from the rest of the pharmacy and from other non-controlled areas, to reduce the risk of introducing viable and non-viable contaminants²¹. It must be physically separated from contiguous areas by walls, doors and pass-throughs.

Use

The clean room is used only for the compounding of non-hazardous sterile preparations.

Contents

The PEC or PECs are installed in the clean room. For non-hazardous compounding, the PECs may be LAFWs or CAIs²².

Table 2

| Functional parameters of the compounding clean room |
|---|
| <p><i>The following functional parameters must be met:</i></p> <ul style="list-style-type: none"> • The clean room must be kept under positive pressure relative to the anteroom and adjacent areas²³. • The pressure differential must be at least 5.0 Pa²⁴ (ideally between 5.0 Pa and 12.5 Pa, equivalent to 0.02 to 0.05 inch water column)^{25, 26} relative to the anteroom²⁷. Smaller pressure differentials may be more difficult to measure and maintain. • ISO Class 7 air quality must be maintained in the clean room under dynamic operating conditions²⁸. • There must be at least 30 or more air changes per hour (ACPH)²⁹. Depending on the size of the room and the number of people working in it, a greater number of ACPH may be required. • The temperature of the clean room must be less than or equal to 20°C, taking into account employees' comfort once all clean room garb (including PPE) has been donned. Medication storage temperatures must not exceed 25°C. <p>Note: There is no requirement for relative humidity; refer to the recommendations of the Canadian Society of Hospital Pharmacists³⁰. See also the pressure diagram for the anteroom and clean room (Figure 1).</p> <p>ISO = International Organization for Standardization; PPE = personal protective equipment.</p> |

21 United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013. pp. 372-3.

22 United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013. pp. 372-3.

23 United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. In: *USP pharmacists' pharmacopeia 2008-2009*. Suppl. 2. Rockville, MD: USP; 2009. p. 44.

24 Direction de l'expertise et de la normalisation. Répertoire des guides de planification immobilière : aires réservées aux préparations stériles – Unité de pharmacie. Québec, QC : Ministère de la santé et des services sociaux, Publications du Québec ; 2013. p. 16.

25 Health Canada, Health Products and Food Branch Inspectorate. *Good manufacturing practices (GMP) guidelines – 2009 edition, Version 2*. GUI-0001. Ottawa, ON: Health Canada; 2009, revised 2011 Mar 4. p. 74. Available from: <http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui-0001-eng.php>

26 United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013. pp. 372-3.

27 United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013. pp. 372-3.

28 United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013. pp. 372-3.

29 International Organization for Standardization (ISO). *ISO 14644-4 Cleanrooms and associated controlled environments – Part 4: Design, construction and start-up*. Geneva, Switzerland: ISO; 2001.

30 Canadian Society of Hospital Pharmacists (CSHP). *Compounding: guidelines for pharmacies*. Ottawa, ON: CSHP; 2014. p. 52.



Given the clothing that compounding personnel are required to wear, the clean room must be maintained at a temperature that will ensure their comfort and allow them to do their work conscientiously. These conditions increase the safety of the aseptic compounding process and minimize skin desquamation.

Access to the clean room is restricted to personnel with specific responsibilities in the clean room.

To enable verification of activities, one or more observation windows must be installed. Such windows reduce the number of times that individuals must enter and exit the clean room. They also ensure the safety of compounding and other personnel.

Anteroom³¹

The anteroom is located between the clean room and the non-controlled areas of the pharmacy, acting as a transition space. The anteroom has two doors.

The anteroom helps to maintain the pressure differential in the clean room. It must therefore be adjacent to the clean room, separate from the rest of the pharmacy and fully enclosed, to provide the required seal and to meet and maintain the desired specifications. Users usually enter the anteroom from the pharmacy.

The anteroom is separated into two spaces by a visible demarcation line:

- a space or area referred to as “dirty,” located at the entrance to the anteroom, in the section adjacent to the non-controlled area;
- a space or area referred to as “clean,” adjacent to the dirty area on one side and the clean room on the other.

It is important to take these “clean” and “dirty” areas into account when traversing the anteroom and when donning and removing PPE.

The functional parameters of the anteroom for the compounding of non-hazardous sterile preparations are presented in Table 3.

Use

The anteroom is the location for activities with higher generation of particulates, such as garbing, hand hygiene, labelling and staging of components.

Activity in the anteroom shall be kept to a minimum and shall be limited to those activities that are essential to or that directly support the work undertaken in the clean room.

Access of supplies, equipment and personnel into the clean room shall be through the anteroom. No supplies, equipment or personnel shall enter into the clean room from a non-controlled area.

Contents

The contents of the anteroom must be limited to facilitate maintenance and to maintain the target ISO air quality classification.

31 United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013. p. 372-3.



The anteroom must contain the following items:

- PPE, placed in the correct order to allow users to follow the correct garbing sequence (*see* section 5.3.3.3 for a description of PPE and section 6.6.2.2 for garbing sequence);
- hands-free sink, ideally made of stainless steel or other material not harmed by cleaning products and large enough to allow users to wash their hands and forearms without touching the sides of the sink, with minimal splashing;
- soap dispenser (cartridge or disposable, non-refillable unit);
- nail picks;
- alcohol-based hand rub (ABHR) with persistent activity and its dispenser;
- hand-drying system:
 - lint-free towels (preferred) with a dispenser
 - air hand dryer designed specifically for use in a controlled area (i.e., the anteroom)
- mirror or other means to verify garbing;
- clock;
- waste container;
- eyewash station³², if available (if not located in the anteroom, the eyewash station must be installed nearby);
- pass-through for transferring products into the clean room and/or a cart reserved for use in the “clean” area of the anteroom and the clean room.

Supplies

In principle, supplies are not kept in the clean room. The supplies, drugs, labels and other items required for each preparation or batch are gathered and assembled in the anteroom and placed in a bin or tray for entry into the clean room at the time of compounding.

A balance must be established between the need for supplies in the anteroom and the need to leave the anteroom to obtain supplies not available there. If applicable, steps must be taken to maintain the anteroom’s ISO air quality classification.

Other essential equipment may be stored in the anteroom as long as the anteroom’s ISO air quality classification is maintained.

The use of equipment in the anteroom and the clean room is permitted as long as the use of such equipment does not increase the generation of viable or non-viable particles within the rooms.

³² Canadian Centre for Occupational Health and Safety (CCOHS). Emergency showers and eyewash stations. Hamilton, ON; CCOHS; 2010. Available from: http://www.ccohs.ca/oshanswers/safety_haz/emerg_showers.html



Table 3**Functional parameters of the anteroom for the compounding of non-hazardous sterile preparations*****The following functional parameters must be met:***

- The anteroom must be kept under positive pressure relative to the non-controlled area adjacent to the anteroom.
- The pressure differential must be at least 5.0 Pa³³ (ideally between 5.0 Pa and 12.5 Pa, equivalent to 0.02 to 0.05 inch water column) relative to the non-controlled area adjacent to the anteroom. Smaller pressure differentials may be more difficult to measure and maintain.
- A notification system must be installed in each pressure monitor to alert pharmacy personnel when pressure differentials deviate from specifications.
- ISO Class 8 air quality must be maintained in the anteroom under dynamic operating conditions, unless the anteroom is also supporting a hazardous drug clean room, in which case ISO class 7 air quality must be maintained.
- There must be at least 20 air changes per hour (ACPH)³⁴. Depending on the size of the room and the number of people working in it, a greater number of ACPH may be required.
- The temperature of the anteroom must be less than or equal to 20°C, taking into account employees' comfort once all clean room garb (included PPE) has been donned. Medication storage temperatures must not exceed 25°C.

Note: There is no requirement for relative humidity; refer to the recommendations of the Canadian Society of Hospital Pharmacists³⁵. See also the pressure diagram for the anteroom and clean room (Figure 1).

ISO = International Organization for Standardization; PPE = personal protective equipment.

The anteroom has two doors; one door between the clean room and the anteroom and the other door between the anteroom and the non-controlled area. The pharmacy must have a process that allows only one door to be open at a time (i.e., to prevent both doors from being open at the same time).

The door between the clean room and the anteroom and the door between the anteroom and the non-controlled area must have windows to prevent accidents involving personnel entering or leaving through the doors.

Horizontal surfaces must be cleaned daily; therefore, their presence in the anteroom must be kept to a minimum, to avoid unduly increasing the workload for cleaning and disinfecting personnel.

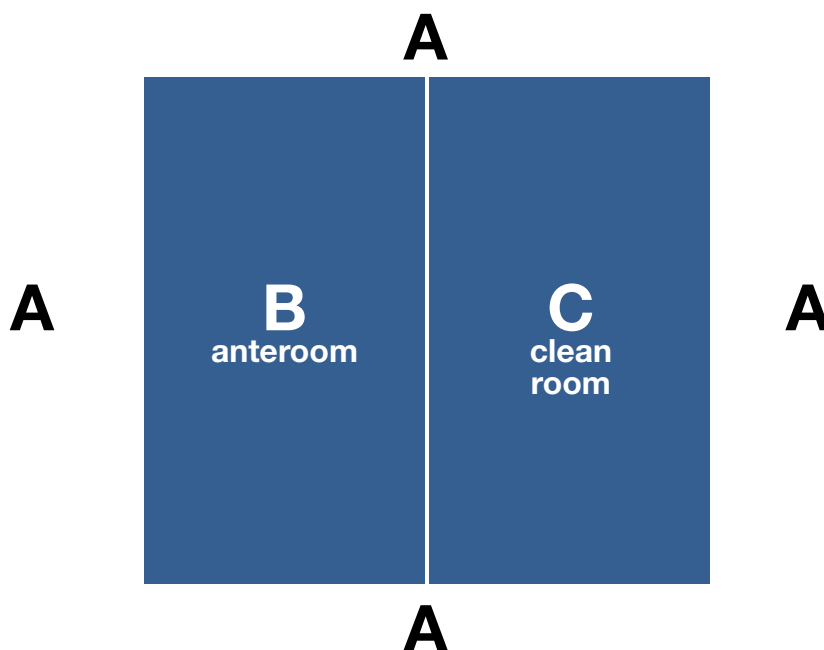
33 Direction de l'expertise et de la normalisation. Répertoire des guides de planification immobilière : aires réservées aux préparations stériles – Unité de pharmacie. Québec, QC: Ministère de la santé et des services sociaux, Publications du Québec ; 2013. p. 16.

34 International Organization for Standardization (ISO). *ISO 14644-4 Cleanrooms and associated controlled environments – Part 4: Design, construction and start-up*. Geneva, Switzerland: ISO; 2001.

35 Canadian Society of Hospital Pharmacists (CSHP). *Compounding: guidelines for pharmacies*. Ottawa, ON: CSHP; 2014. p. 52.



Figure 1: Pressure diagram



| Pressure differentials: | | |
|---|---|---|
| Pressure differentials to be maintained at all times: | 1) | $12.5 \text{ Pa} \geq (P_C - P_B) \geq 5.0$ |
| | 2) | $12.5 \text{ Pa} \geq (P_B - P_A) \geq 5.0$ |
| Legend: | | |
| | A = facilities environment | |
| | B = anteroom | |
| | C = clean room | |
| | P = pressure | |
| | Pa = pascal (SI unit of measure for pressure) | |

Area for unpacking supplies

Space should be provided for unpacking supplies.

To limit the presence of dust and particles in the anteroom, supplies must be removed from cardboard boxes outside the anteroom³⁶ and disinfected with a sporicidal agent before being moved into the anteroom.

5.3.2.6 Shared facilities

Compounding of non-hazardous and hazardous sterile preparations

Facilities in community pharmacies or health care facilities that compound both non-hazardous and hazardous sterile preparations must have two clean rooms: one for the compounding of non-hazardous sterile preparations and the other for the compounding of hazardous sterile preparations, as well an anteroom for each type of compounding.

³⁶ United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013. p. 375.



In some community pharmacies and smaller health care facilities, space may be limited. Although separate clean rooms are still required for each type of preparation (i.e., one for non-hazardous sterile preparations and the other for hazardous sterile preparations), they may share a single anteroom.

This layout is not recommended, but if space constraints dictate that facilities for compounding non-hazardous and hazardous sterile preparations share an anteroom, the conditions described in the following subsections must be met.

Clean room for the compounding of non-hazardous sterile preparations

The functional parameters of the clean room for this type of facility are the same as those required for the compounding clean room described in section 5.3.2.5.

Clean room for the compounding of hazardous sterile preparations

The functional parameters of the clean room for this type of facility are the same as those required for the compounding clean room described in the companion document, “Model Standards for Pharmacy Compounding of Hazardous Sterile Preparations.”

Shared anteroom

The sole anteroom is connected to both clean rooms for the compounding of sterile preparations (non-hazardous and hazardous) and is shared for hand hygiene and garbing activities of personnel working in the two clean rooms. The functional parameters of the shared anteroom for the compounding of non-hazardous and hazardous sterile preparations are presented in Table 4.

In this case, the anteroom is separated into two spaces (areas) by a demarcation line:

- a space or area referred to as “dirty,” located adjacent to the non-controlled areas, at the entrance to the anteroom;
- a space or area referred to as “clean but possibly chemically contaminated,” located adjacent to the clean room for the compounding of non-hazardous sterile preparations and the clean room for the compounding of hazardous sterile preparations.

If there is enough space, the clean area of the anteroom may be further divided into two areas:

- a “clean but chemically contaminated” space or area *adjacent to the clean room for the compounding of hazardous sterile preparations;*
- a “clean and not chemically contaminated” space or area *adjacent to the clean room for the compounding of non-hazardous sterile preparations.*

It is important to take these “clean” and “dirty” areas into account when traversing the anteroom and when donning and removing PPE. Activities in a shared anteroom are limited to hand washing and donning of PPE. No drugs are stored in a shared anteroom.



Table 4**Functional parameters of a shared anteroom for the compounding of non-hazardous and hazardous sterile preparations*****The following functional parameters must be met:***

- The anteroom must be kept under positive pressure relative to both the clean room for compounding of hazardous drugs and non-controlled areas adjacent to the anteroom.
- The pressure differential must be at least 5.0 Pa³⁷ (equivalent to 0.02 inch water column) relative to the adjacent areas.
- A notification system must be installed in each pressure monitor to alert pharmacy personnel when pressure differentials deviate from specifications.
- ISO Class 7 air quality must be maintained in the anteroom under dynamic operating conditions³⁸.
- There must be at least 30 air changes per hour (ACPH)³⁹. Depending on the size of the room and the number of people working in it, a greater number of ACPH may be required.
- The temperature of the anteroom must be less than or equal to 20°C, taking into account employees' comfort once all clean room garb (including PPE) has been donned. Medication storage temperatures must not exceed 25°C.

Note: There is no requirement for relative humidity; refer to the recommendations of the Canadian Society of Hospital Pharmacists⁴⁰.

ISO = International Organization for Standardization; PPE = personal protective equipment.

The air diffusers must be positioned so that the particle stream is directed toward the “dirty” area of the anteroom.

All air flowing within the shared anteroom must be exhausted to the exterior of the building. The air flowing into the anteroom must not be recycled.

5.3.2.7 All other facilities

The specifications recommended in the previous sections are similar to the recommendations for facilities laid out in General Chapter <797> of the USP–NF⁴¹ for compounding rooms used for the preparation of non-hazardous sterile products.

5.3.2.8 Materials and finishes

The surfaces of ceilings, walls, floors, doors, door frames, shelves, counters and cabinets in controlled areas must be smooth, impervious, non-friable, free from cracks and crevices, non-porous and resistant to damage from cleaning and disinfecting products. These characteristics make them easy to clean and disinfect, as well as preventing the accumulation of microorganisms and non-viable contaminants.

Dust-collecting overhangs, such as door sills, utility pipes, windowsills, window curtains and window blinds, must be avoided.

37 Direction de l'expertise et de la normalisation. Répertoire des guides de planification immobilière : aires réservées aux préparations stériles – Unité de pharmacie. Québec, QC: Ministère de la santé et des services sociaux, Publications du Québec ; 2013. pp. 18, 22.

38 United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013. p. 368.

39 International Organization for Standardization (ISO). *ISO 14644-4 Cleanrooms and associated controlled environments – Part 4: Design, construction and start-up*. Geneva, Switzerland: ISO; 2001.

40 Canadian Society of Hospital Pharmacists (CSHP). *Compounding: guidelines for pharmacies*. Ottawa, ON: CSHP; 2014. p. 52.

41 United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013. pp. 368, 372, 373. USP, response provided by USP for these facilities, March 21, 2012.



Ceilings

In controlled areas (clean room and anteroom), ceilings must have the following characteristics:

- Ceilings must be constructed of smooth, impervious, non-friable, non-porous, waterproof materials resistant to damage from cleaning and disinfecting products. All joints must be sealed.
- In the clean room and the anteroom, joints between the ceiling and walls should be free of sharp corners where foreign substances could accumulate⁴². This can be achieved by coving the ceiling to the wall or by caulking.
- If a recessed panel ceiling must be installed, the panels must be specifically designed for use in a clean room.
- If a conventional recessed panel ceiling is installed⁴³, the panels must be impregnated with polymer to make them impermeable and hydrophobic, and the edges must be coated with clean room silicone to seal them to the support frame⁴⁴. The tiles on this type of ceiling require periodic preventive sealing because the sealer eventually dries out. When facilities undergo certification, this type of ceiling must be tested for tightness. This type of ceiling is not recommended for new facilities.
- In all rooms reserved for the compounding of sterile preparations, any holes, cracks or breakage in ceilings must be repaired and sealed at the earliest opportunity.

Walls

In controlled areas (clean room and anteroom), the walls must have the following characteristics:

- The walls must be constructed of smooth, impervious, non-friable, non-porous, waterproof materials resistant to damage from cleaning and disinfecting products, such as gypsum board coated with epoxy paint, thick polymer panels or glass panels. All joints must be sealed. In locations at higher risk of breakage, stainless steel plates or other hard, non-porous material should be installed to prevent walls from being damaged when furniture is moved.
- In all rooms reserved for the compounding of sterile preparations, any holes, cracks or breakage in walls must be repaired and sealed at the earliest opportunity.

Floors

In controlled areas (clean room and anteroom), the floors must have the following characteristics:

- Flooring must be flat, smooth, impervious, non-friable, non-porous, sealed and resistant to damage from cleaning and disinfecting products. Any breakage must be repaired and sealed immediately.
- In the clean room and anteroom, the floor must be coved up the side wall, at least 10–15 cm.
- There must be no carpets, rugs, “sticky mats” or antifatigue mats⁴⁵.

42 Health Canada, Health Products and Food Branch Inspectorate. *Good manufacturing practices (GMP) guidelines – 2009 edition, Version 2*. GUI-0001. Ottawa, ON: Health Canada; 2009, revised 2011 Mar 4. p. 10. Available from: <http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui-0001-eng.php>

43 United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013. p. 372-3.

44 United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013. p. 372-3.

45 Canadian Centre for Occupational Health and Safety (CCOHS). Anti-fatigue mats. Hamilton, ON: CCOHS; 1997, confirmed current 2006. Available from: <http://www.ccohs.ca/oshanswers/ergonomics/mats.html>



5.3.2.9 Accessories

Ceiling fixtures

In controlled areas (clean room and anteroom), ceiling fixtures must be recessed and flush-mounted. Their external surfaces, whether made of glass or other material, must be washable, smooth and sealed.

Plumbing

Water sources, sinks and drains must not be located in a clean room but are permitted in the anteroom.

Functional parameter control systems

Control systems indicating the temperature and differential pressure between controlled areas should be positioned together. Functional parameters require constant monitoring, so the controls should be installed where it is easy for personnel to take frequent readings (*see* section 7.3).

Control systems must be connected to a notification system to alert personnel when operating parameters are outside preset limits. This allows personnel to make the necessary adjustments quickly while avoiding contamination of controlled areas and the problems that may result, including service interruption.

Instruments for measuring differential pressure between controlled areas must be calibrated at least once a year or as recommended by the manufacturer.

5.3.2.10 Work surfaces and furniture

Work surfaces

Work surfaces and furniture must be constructed of smooth, impervious, non-friable and non-porous materials, preferably stainless steel. Any material used for work surfaces must be able to withstand repeated cleaning and disinfecting and be resistant to damage from cleaning and disinfecting products. Any breakage must be repaired and sealed at the earliest opportunity.

A horizontal surface such as a shelf or a cart should be available in the clean room to aid in donning gloves. Gloves shall not be donned within the ISO Class 5 PEC.

Furniture

All furniture in the clean room and anteroom, as well as the floor and wall surfaces, must be designed and placed to facilitate cleaning and disinfecting.

All movable furniture must be cleaned and disinfected before it is placed in the clean room.

Chairs used in controlled areas must be made of smooth, non-friable, non-porous, washable materials that are resistant to damage from cleaning and disinfecting products. Some chairs are specifically designed for use in clean rooms, and these should be the preferred choice.

Pass-through and/or cart

A pass-through should be installed for transferring products into and out of the clean room. The pass-through should be sealed and made of stainless steel or a smooth, non-porous, antistatic material resistant to damage from cleaning and disinfecting products.

It is recommended that the pass-through be equipped with an interlocking system that prevents both doors from being open at the same time. If an interlocking system is not available, a door-opening procedure must be implemented whereby only one door is open at a time.



If there is no pass-through, the clean room cart may be used to transport materials from the “clean” area of the anteroom into the clean room.

5.3.2.11 Signage

Each room must be identified with appropriate and informative signs (e.g., pictograms depicting the need for special care, hazards, restricted access, dress code).

5.3.2.12 Facility maintenance

Facility maintenance involves keeping the compounding areas operational within specifications or bringing facility systems, including HVAC, back to satisfactory operating conditions after an interruption. Maintenance must be also performed on equipment within the facility.

Facility maintenance activities must be recorded in the general maintenance log.

Filters and pre-filters

The efficiency of HEPA filters in the ventilation system must be tested during facility certification (at least every 6 months), and filters must be replaced periodically as recommended by the manufacturer.

5.3.3 Equipment

5.3.3.1 Primary Engineering Control⁴⁶

The PEC ensures an ISO Class 5 air quality environment for the exposure of critical sites when sterile preparations are being compounded. PEC options for non-hazardous sterile preparations include LAFWs and CAIs. The PEC is positioned in the clean room.

Before a PEC is used,

- personnel must read and understand the user’s manual;
- the PEC must be installed according to the manufacturer’s recommendations and certified by a qualified certifier (*see* Appendix 5);
- cleaning and disinfection must be performed according to specifications in section 6.6.4.

The sterile compounding supervisor must ensure that the certification is completed according to certification standards currently in force (*see* Appendix 6).

A PEC must operate continuously⁴⁷ during every sterile compounding activity. If the PEC has been turned off, it must be allowed to run for at least 30 minutes, or as recommended by the manufacturer, before cleaning, disinfection and compounding of sterile preparations are undertaken^{48,49}.

The PEC must provide a work area with unidirectional airflow and quality meeting ISO Class 5 or better under dynamic operating conditions.

The working surface of the PEC must be resistant to damage from cleaning and disinfecting products and must be changed if it becomes damaged.

46 United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013. pp. 362-4, 372-4.

47 United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013. p. 379-80.

48 United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013. p. 379-80.

49 Occupational Safety and Health Administration (OSHA). *OSHA technical manual (OTM): controlling occupational exposure to hazardous drugs*. Section VI, Chapter 2. Washington, DC: US Department of Labor; 1999. Available from: https://www.osha.gov/dts/osta/otm/otm_vi/otm_vi_2.html



If a CAI is in use, the recovery time recommended by the manufacturer (i.e., the waiting time required to achieve ISO Class 5 air quality after materials have been transferred, before aseptic processing is started) must be observed when transferring products from the clean room to the manipulation area.

Location of primary engineering control and other furniture

The PEC and other pieces of furniture should be positioned to avoid interfering with facility ventilation systems.^{50, 51, 52}

To facilitate cleaning and disinfecting activities, such as cleaning the exterior of the PEC, and to avoid interfering with the operation of the PEC, there must be sufficient clearance around the PEC (usually 0.3 m⁵³)⁵⁴. Some types of PEC can be built into the wall and sealed or wall-mounted and sealed, but this type of installation is not possible with other types. When positioning a PEC, the manufacturer's recommendations must be strictly followed to avoid interfering with normal operation. During certification, a smoke test under dynamic conditions must be used to validate proper operation.

LAFW^{55, 56, 57}

The LAFW must be positioned in an ISO Class 7 clean room that is adjacent to an ISO Class 8 anteroom and must not be placed near doors or other sources of drafts that might adversely affect unidirectional airflow.

If multiple LAFWs are used, they must be positioned to prevent interference with one another.

CAI^{58, 59, 60}

The CAI must be positioned in an ISO Class 7 clean room adjacent to an ISO Class 8 anteroom.

However, the CAI may be positioned in an environment where the air particles exceed ISO Class 7 if all of the following conditions are met:

- The CAI maintains an ISO Class 5 environment (*see* Table 1) at all times during compounding, including when ingredients, equipment and devices are being transferred into and out of the CAI.
- Particulate sampling from 15 to 30 cm upstream of the critical exposure site within the CAI shows ISO Class 5 air quality during compounding.

50 United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013.

51 Peters GF, McKeon MR, Weiss WT. Potentials for airborne contamination in turbulent- and unidirectional-airflow compounding aseptic isolators. *Am J Health Syst Pharm* 2007;64(6):622-31.

52 Controlled Environment Testing Association (CETA). *CETA compounding isolator testing guide: CAG-002-2006*. Raleigh, NC: CETA; 2006, revised 2008 Dec 8. Available from: <http://www.cetainternational.org/reference/CETACompoundingIsolatorTestingGuide2006.pdf>

53 Association paritaire pour la santé et la sécurité du travail du secteur affaires sociales (ASSTSAS). *Prevention guide — safe handling of hazardous drugs*. Montréal, QC: ASSTSAS; 2008. pp. 7-9. Available from: <https://www.irsst.qc.ca/media/documents/PublIRSST/CG-002.pdf>

54 Direction de l'expertise et de la normalisation. Répertoire des guides de planification immobilière : aires réservées aux préparations stériles – Unité de pharmacie. Québec, QC: Ministère de la santé et des services sociaux, Publications du Québec ; 2013. p. 17.

55 United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013.

56 Peters GF, McKeon MR, Weiss WT. Potentials for airborne contamination in turbulent- and unidirectional-airflow compounding aseptic isolators. *Am J Health Syst Pharm* 2007;64(6):622-31.

57 Controlled Environment Testing Association (CETA). *CETA compounding isolator testing guide: CAG-002-2006*. Raleigh, NC: CETA; 2006, revised 2008 Dec 8. Available from: <http://www.cetainternational.org/reference/CETACompoundingIsolatorTestingGuide2006.pdf>

58 United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013.

59 Peters GF, McKeon MR, Weiss WT. Potentials for airborne contamination in turbulent- and unidirectional-airflow compounding aseptic isolators. *Am J Health Syst Pharm* 2007;64(6):622-31.

60 Controlled Environment Testing Association (CETA). *CETA compounding isolator testing guide: CAG-002-2006*. Raleigh, NC: CETA; 2006, revised 2008 Dec 8. Available from: <http://www.cetainternational.org/reference/CETACompoundingIsolatorTestingGuide2006.pdf>



- Particulate sampling conducted as close as possible to the doors when materials are being transferred, without obstructing the passageway, shows no more than 3520 particles (0.5 µm diameter or larger) per cubic metre of air (ISO Class 5) in the CAI.

The sterile compounding supervisor must obtain the following information from the manufacturer:

- documentation indicating that the CAI meets established standards when installed in an environment where the number of particles exceeds ISO Class 7 specifications;
- the waiting time required to achieve ISO Class 5 air quality after materials have been transferred, before aseptic processing is started (i.e., the recovery time).

Maintenance of primary engineering control

PECs must be maintained in accordance with the manufacturer's recommendations but certified according to the testing standards detailed in the Controlled Environment Testing Association (CETA) application guide CAG-003 (current version).

Each PEC must be certified⁶¹

- every 6 months;
- when relocated;
- after major repairs;
- when viable air sampling indicates that the PEC may not be in compliance with specifications.

If a PEC on wheels is moved (e.g., to clean under the wheels) and then moved back to exactly the same place, re-certification is not necessary.

PEC pre-filters must be accessible. They should be inspected every 6 months and replaced if necessary or as recommended by the manufacturer. Washable pre-filters must not be used.

HEPA filters shall be verified during installation and certification to ensure there are no leaks or damage to the filters after they have been transported or installed.

Preventive maintenance for PECs and other equipment must be performed when no compounding is in progress, before cleaning and disinfection operations.

All PEC maintenance and certification, including maintenance of filters and pre-filters, must be documented in the general maintenance log (paper-based or computerized).

The sterile compounding supervisor must ensure that PEC maintenance and certification have been performed. The supervisor must review the results or ensure that the results have been reviewed and corrective measures taken, as appropriate. The supervisor must sign the maintenance form or log.

5.3.3.2 Other devices, instruments or accessories related to the compounding of non-hazardous sterile preparations

Equipment used to compound sterile preparations must be clean and disinfected with germicidal detergent, followed by a sterile disinfectant such as 70% isopropyl alcohol. Equipment must be made of materials resistant to damage from cleaning and disinfecting products.

61 United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013. p. 373.



The decision to place equipment, instruments or accessories not directly related to sterile-preparation compounding (carts, cabinets, computer monitors, etc.) in the clean room depends on whether such placement will have an impact on maintaining environmental conditions in the clean room (air quality control, surface sampling, etc.)⁶².

The use of equipment in the anteroom and the clean room is permitted as long as the use of such equipment does not increase the generation of viable or non-viable particles within the rooms.

All necessary devices, instruments and accessories must be cleaned and disinfected before being placed in a controlled area. Devices, instruments and accessories to be used in controlled areas should not be removed without good reason.

Maintenance of devices, instruments and accessories must be recorded in the general maintenance log.

Automated compounding device and balance

The automated compounding device (ACD) must be positioned in the PEC such that compounding occurs while critical sites are exposed to first air.

If the ACD is a peristaltic pump, this device must be calibrated between batches.

The ACD must be calibrated at least once a day (after cleaning), then as needed, according to the manufacturer's recommendations. The balance must be calibrated before each use, after it is moved, after cleaning and as needed, according to the manufacturer's recommendations.

The ACD and the balance are to be maintained according to the manufacturer's recommendations.

The results of calibration must be entered in the preparation log, general maintenance log or some other form of documentation (e.g., mix check report) for each batch, at a minimum.

Carts

If carts are used, one cart must be reserved for the "dirty" area of the anteroom and must remain there⁶³.

A second cart, dedicated to the "clean" area of the anteroom, may enter the clean room⁶⁴.

Supplies are disinfected while they are being transferred onto the clean room cart.

Carts used to bring supplies into the anteroom from outside the controlled area shall not cross the demarcation line. Likewise, carts taken into the anteroom from the clean room shall not be moved beyond the clean side of the demarcation line.

If the anteroom is shared, one cart must be reserved for the "clean but chemically contaminated" area and another for the "clean and not chemically contaminated" area.

Carts should be made of stainless steel or very good quality plastic, should be smooth, non-friable, non-porous and resistant to damage from cleaning and disinfecting products, and should have easy-to-clean casters.

Carts should be cleaned and disinfected daily.

62 United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013. p. 372.

63 United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013. p. 379.

64 United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013. p. 379.



Refrigerator and freezer

Choice

The refrigerator and freezer used to store medications must be commercial biomedical grade units^{65, 66, 67}. Domestic refrigerators and freezers must not be used.

Use and placement

Refrigerators and freezers used for storing medications must not be used to store food. Ideally, refrigerators and freezers are placed outside controlled areas. Depending on workflow, refrigerators may be placed in anterooms, provided there is control of particulates through the use of air returns and provided the number of air changes per hour is sufficient to maintain the required ISO air quality classification.

Pass-through refrigerators

Refrigerators with doors on two sides (pass-through refrigerators) may be used to store sterile products, provided they are designed for clean rooms and the refrigeration system is not located on the clean room side. If such a refrigerator is installed, the sterile compounding supervisor is responsible for ensuring that the required characteristics for any compounding rooms affected by its installation are met under operating conditions.

Temperature and temperature control

The tested storage temperature in these units must meet the following parameters:

- controlled refrigeration temperature: 2°C to 8°C
- controlled freezing temperature: -25°C to -10°C

Accurate temperature probes (gauges or sensors) must be installed to indicate the actual temperature. A continuous temperature recorder built into each unit is the preferred option.

A notification system must be installed in each refrigerator and freezer to alert pharmacy personnel when temperatures deviate from specifications.

Refrigerator and freezer temperature readings must be recorded on a form stored in the general maintenance log, unless the units are equipped with a continuous temperature recorder. In the latter situation, the data recorded by this device must also be verified and stored.

Temperature probes must be maintained and calibrated at least once a year or in accordance with the manufacturer's instructions. Calibration of these instruments must be noted in the general maintenance log.

Incubator

An incubator is used to maintain a constant temperature for the culture of microorganisms.

The incubation temperature must be controlled (20°C to 25°C or 30°C to 35°C, depending on the culture medium and incubation period).

65 Health Canada, Health Products and Food Branch Inspectorate. *Guidelines for temperature control of drug products during storage and transportation*. GUI-0069. Ottawa, ON: Health Canada; 2011. Available from: <http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui-0069-eng.php>

66 Public Health Agency of Canada (PHAC). *National vaccine storage and handling guidelines for immunization providers*. Ottawa, ON: PHAC; 2007. p. 19.

67 *Drug and Pharmacies Regulation Act*, R.S.O. 1990, c. H.4. Available from: <http://www.ontario.ca/laws/statute/90h04>



When the incubator is in operation, the incubator temperature must be read and recorded in the general maintenance log at least once a day.

The incubator must be calibrated and maintained according to the manufacturer's recommendations.

The incubator must not be placed in the clean room or the anteroom. It may be located in the general pharmacy or another room nearby.

Camera and computer equipment

Audio-visual and computer equipment used for verification during compounding (camera, monitor, pedal system) is allowed in the clean room under certain conditions. Preference must be given to audio-visual and computer equipment that features "hands-free" operation and that is made of smooth, non-porous, cleanable materials with low particulate emission and resistance to damage from cleaning and disinfecting products.

The installation and use of accessories (monitor, camera) that can be maintained and repaired without compromising the controlled area is preferred.

Equipment cables must be covered to facilitate cleaning.

Communication system

A functional communication system (intercom, telephone or other) may be installed to allow verbal communication between the various controlled areas and the pharmacy. These devices should be used in "hands-free" mode, must be easy to clean and disinfect and must be resistant to damage from cleaning and disinfecting products. Personal electronic devices or accessories (cell phone, iPods, earbuds) are not permitted in the anteroom or clean room.

Waste containers

A sufficient number of easy-to-clean waste containers of suitable size and made of materials resistant to damage from cleaning and disinfecting products must be available.

The waste shall be collected in plastic bags and removed with minimal agitation. The waste containers must be emptied and cleaned at least once a day, at a time when no compounding is occurring.

5.3.3.3 Personal protective equipment and clothing

Compounding personnel and anyone else who accesses controlled areas must wear appropriate protective clothing, as described in Table 5.



Table 5

| Personal protective equipment (PPE) for the compounding of non-hazardous sterile preparations |
|---|
| <p>PPE to be worn⁶⁸ for the compounding of non-hazardous sterile preparations and when accessing facilities for the compounding of non-hazardous sterile preparations includes the following:</p> <ul style="list-style-type: none"> • pair of shoe covers or dedicated shoes • hair cover • beard cover (if applicable) • surgical mask • non-shedding protective gown (enclosed at the neck and with sleeves that fit snugly around the wrists) • pair of non-powdered sterile gloves, which must cover the cuffs of the non-shedding gown |

5.3.4 Cleaning and disinfecting in areas reserved for the compounding of non-hazardous sterile preparations

5.3.4.1 General

Cleaning and disinfecting (housekeeping) in the controlled area must be performed to ensure the cleanliness required for the quality and integrity of final sterile preparations⁶⁹.

Cleaning and disinfecting procedures must be strictly adhered to in the clean room and the anteroom.

Policies and procedures for cleaning and disinfecting tasks must be developed, and cleaning and disinfecting personnel must be trained and assessed on correct application of these policies and procedures.

Only trained and qualified cleaning and disinfecting personnel may be allowed to clean the controlled area⁷⁰.

5.3.4.2 Disinfectant

Use of a germicidal disinfectant detergent is required to disinfect all surfaces in a clean room and anteroom. Many types of germicidal disinfectant detergents are acceptable.

The sterile compounding supervisor must

- select an appropriate disinfecting agent for controlled areas, considering mainly its effectiveness and compatibility with materials used for facilities and equipment;
- in health care facilities, take into account the organization's disinfection policies and procedures, following the manufacturer's directions to dilute the disinfectant properly;
- follow the manufacturer's directions regarding required contact time between the disinfectant and the surface to be cleaned.

68 United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013. p. 376-7.

69 United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013. p. 376.

70 United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013. p. 376.



Use of an alternative disinfectant in the rotation is unnecessary. However, the daily use of a germicidal disinfectant should be augmented with weekly (or monthly) use of a sporicidal agent⁷¹.

The material safety data sheets for disinfectants used in the facility must be available on site and easily accessible.

5.3.4.3 Equipment used for cleaning and disinfection and its storage

To avoid cross-contamination and to protect cleaning and disinfecting personnel, equipment must be specifically designated for cleaning areas used for compounding non-hazardous sterile preparations⁷².

Non-shedding⁷³ equipment must be used for cleaning controlled areas.

This equipment (mop heads, towels, etc.) should be disposable. If reusable accessories are used, they must be washed and dried after each use and must be stored in a clean cabinet dedicated to storing this equipment⁷⁴.

If reusable accessories are used, one set of accessories must be dedicated to cleaning ISO Class 5 areas and a separate set dedicated to cleaning ISO Class 7 and 8 areas.

Cleaning equipment and supplies (mop handle, outside of bottles, etc.) must be disinfected before each entry into a controlled area. A cabinet located in the anteroom or nearby must be provided for storing equipment (mop handle, etc.), refills (mop heads, towels) and cleaning products used for cleaning and disinfecting.

5.3.4.4 Garbing of cleaning and disinfecting personnel (housekeeping personnel)

Cleaning and disinfecting personnel must comply with the pharmacy's hand hygiene and garbing procedure before entering sterile compounding areas and performing housekeeping duties. Housekeeping personnel must also don gloves before starting work.

5.3.4.5 Cleaning frequency

The minimum frequency of cleaning and disinfecting in clean rooms and anterooms will be either daily or monthly⁷⁵.

Daily cleaning and disinfecting are required for the following surfaces and areas:

- PEC
- counters
- carts
- floors
- surfaces that are touched frequently (e.g., doorknobs, switches, chairs)

In addition, waste and garbage must be removed daily.

71 United States Pharmacopeial Convention (USP). General chapter <1072>: disinfectants and antisepsis. In: *USP pharmacists' pharmacopeia*. Rockville, MD: USP; 2008-2009.

72 Okeke CC, Allen LV Jr. Considerations for implementing United States Pharmacopeia chapter <797> pharmaceutical compounding – sterile preparations. Part 4: Considerations in selection and uses of disinfectants and antiseptics. *Int J Pharm Compound*. 2007;11(6):492-9.

73 United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013. p. 376.

74 McAteer F. Points to consider for developing a USP-797 compliant cleaning and sanitization program. *Clean Rooms*. 2007;21(8):44,48. Available from: <http://electroiq.com/issue/?issue=2302>

75 United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding – sterile preparations. In: *USP pharmacists' pharmacopeia*. 2nd ed., Suppl. 2. Rockville, MD: USP; 2008. p. S2/47.



Monthly cleaning and disinfecting are required for the following surfaces and areas:

- walls
- ceiling
- shelves
- outer surfaces of the PEC

Cleaning should be performed from the “cleanest” area to the “dirtiest” area (i.e., from the closed end of the clean room toward the anteroom exit).

Forms or schedules used to document cleaning and disinfecting activities, as per established policy, must be retained in the general maintenance log.

5.4 General maintenance log

The general maintenance log (paper-based or computerized) includes all records or forms regarding the following activities:

- cleaning and disinfecting, certification and maintenance of the facility as a whole, certification and maintenance of the PEC and maintenance of other equipment;
- verification of proper operation of equipment and instruments (calibration, refrigerator temperatures, etc.).

All records must be retained as per standards of practice of the respective provincial/territorial regulatory authority and in accordance with the principles of confidentiality.



6. PRODUCT AND PREPARATION REQUIREMENTS

6.1 Beyond-use date and dating methods

6.1.1 Beyond-use dates for preparations

For the purposes of these Model Standards, administration of the compounded sterile preparation must begin before the BUD has passed⁷⁶.

The BUD also specifies the storage time and temperature conditions that must be in effect before administration.

The method used to establish the BUD depends on the type of commercial container (single-dose vial or multiple-dose container) used for the preparation and/or the risk of contamination of the particular preparation.

Where no specific sterility testing is performed for a preparation or batch, the sterile compounding supervisor must assign a BUD on the basis of the following criteria.

The BUD must not exceed the earliest of the dates established by the following two criteria:

- expiration date based on chemical and physical stability^{77, 78, 79} according to reference texts
- storage time related to risk of microbial contamination

To establish a longer BUD, sterility tests must be performed for a given preparation or batch. Preparations must be quarantined while awaiting the results of the sterility test. Preparations may be released once the results of the sterility test are obtained.

The pharmacy's operating procedures must describe the risk assessment process used to establish the BUD and the storage conditions.

6.1.2 Beyond-use dates for commercially available products according to type of container (single-dose vial or multiple-dose container)

During compounding, the use of commercially available products must have priority. More specifically, if a sterile product is commercially available, compounding personnel must not use non-sterile ingredients to compound a sterile preparation.

The BUDs for commercial products specified in the following three subsections (6.1.2.1, 6.1.2.2 and 6.1.2.3) apply when such products are stored in the original package and container.

6.1.2.1 Single-dose vial

- A single-dose vial will be labelled as such by the manufacturer. Single-dose vials include pharmacy bulk vials if the manufacturer has labelled them as single-dose vials.
- If the vial is punctured in a PEC that maintains ISO Class 5 air quality, the BUD is 6 hours⁸⁰.
- Six hours after initial needle puncture, the vial can no longer be used. Once the vial is removed from the ISO Class 5 PEC, it must be discarded.

76 United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013.

77 Trissel LA. *Handbook on injectable drugs*. 17th ed. Bethesda, MD: American Society of Health-System Pharmacists; 2013.

78 King JC. King guide to parenteral admixtures [electronic version]. Napa, CA: King Guide Publications Inc.; [updated quarterly].

79 Trissel LA. Trissel's 2 clinical pharmaceuticals database [electronic database]. Cashiers, NC: TriPharma Communications; [updated regularly].

80 United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013.

- To properly manage risk, a label must be affixed to the vial indicating the time of initial needle puncture.
- The contents of a vial may not be divided for the sole purpose of extending stability.
- If the vial or another single-dose container is opened or punctured in an environment with air quality worse than ISO Class 5, the BUD is 1 hour.

6.1.2.2 Open ampoule

- No storage of an open ampoule is permitted; as such, no BUD applies.

6.1.2.3 Multiple-dose container (e.g., vial)

- A multiple-dose container will be labelled as such by the manufacturer.
- Multiple-dose containers usually contain a preservative.
- The BUD is 28 days, unless otherwise specified by the manufacturer.
- If there is visible contamination before 28 days (or the manufacturer's expiry date), the container must be discarded.

6.1.3 Beyond-use dates according to risk of microbial contamination

Compounded medications are at risk of microbial contamination, with the passage of time and changes in temperature allowing unacceptable levels of microbial colonization. Microorganisms undergo various phases of growth. After an initial or stationary phase (phase 1), which varies by species, bacteria replicate within 20 to 30 minutes (phase 2 growth). Once contamination occurs, bacterial growth increases rapidly starting 6 hours after the onset of contamination⁸¹.

The BUD is based on the risk that a preparation may be contaminated (Table 6). Once the level of risk is established, refer to Table 7 for the BUD.

Levels of risk for microbial contamination apply to preparations compounded in a compliant, certified PEC that maintains ISO Class 5 air quality or better and that is located in an ISO Class 7 clean room or a compliant, certified CAI that meets the criteria specified in section 5.3.3.1 when placed in environments with particle counts exceeding ISO Class 7.

Sterile unit

The concept of a “sterile unit” is used to specify certain criteria for establishing the BUD.

A sterile unit is a vial, ampoule or bag of drug or diluent. The following examples illustrate the concept:

- 1 bag of solute represents 1 “sterile unit.”
- 2 vials of cefazolin represent 2 “sterile units.”
- 1 vial of sterile water for injection represents 1 “sterile unit.”

81 Cundell AM. USP Committee on Analytical Microbiology — stimuli to the revision process. *Pharmacoepial Forum*. 2002;28(6).



Table 6

| Contamination risk levels ^{82, 83} | | |
|---|---|---|
| Low | Medium | High |
| <ul style="list-style-type: none"> Final product compounded using up to 3 “sterile units” No more than 2 septum punctures at the injection site for each sterile unit Simple aseptic transfer technique Drug prepared for one patient (patient-specific dose) | <ul style="list-style-type: none"> Final product compounded using 4 or more “sterile units” Complex manipulations Prolonged preparation time Batch preparations (preparing more than one unit of the same composition during one compounding session) | <ul style="list-style-type: none"> Non-sterile ingredients or equipment used before terminal sterilization Non-sterile preparations, containing water, stored for more than 6 hours before terminal sterilization Improper garbing or gloving by compounding personnel |

Table 7

| Beyond-use dates (BUDs) for compounded sterile preparations, according to risk of microbial contamination ⁸⁴ | | | |
|---|--------------------------------|------------------------------|-------------------------|
| Risk of contamination | BUD without sterility testing | | |
| | At controlled room temperature | With storage in refrigerator | With storage in freezer |
| Low | 48 hours | 14 days | 45 days |
| Medium | 30 hours | 9 days | 45 days |
| High | 24 hours | 3 days | 45 days |

Administration of the compounded sterile preparation must begin before the BUD has passed.

High-risk preparations must always be sterilized, and the BUDs in the high-risk row of Table 7 apply to high-risk *sterile* preparations.

Sterility test and bacterial endotoxin test⁸⁵

A sterility test via membrane filtration and a bacterial endotoxin test must be performed for high-risk sterile preparations (*see* Table 6) in the following situations:

- when sterile preparations are compounded in batches of over 25 identical units;
- when there has been more than 12 hours of exposure time at a temperature between 2°C and 8°C before sterilization;
- when there has been more than 6 hours of exposure time at a temperature above 8°C before sterilization.

6.1.4 Beyond-use dates for immediate-use preparations

Pharmacy departments and community pharmacies that provide sterile-preparation compounding services must meet the requirements specified in these Model Standards, specifically those related to adequate facilities and equipment, compliance with garbing requirements and application of stringent housekeeping and aseptic techniques.

82 United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013.

83 American Society of Health-System Pharmacists (ASHP). The ASHP discussion guide on USP chapter <797> for compounding *sterile preparations*. Summary of revisions to USP chapter <797>. Bethesda, MD: ASHP with Baxter Healthcare Corporation; 2008.

84 United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013.

85 United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013. p. 361.

In health care facilities, a pharmacy department that provides compounded sterile preparation services must ensure that compounded doses are ready to be administered without further handling by another health care professional and must develop its services in accordance with this requirement.

Compounded sterile preparations prepared for immediate use in the patient's room or on patient care units must comply with the following conditions:

- Compounding is performed only when the situation is critical, with a requirement for immediate administration to the patient.
- The preparation does not exceed 3 “sterile units.”
- The preparation does not contain any hazardous drugs (e.g., chemotherapeutic agents).
- For each sterile unit used, there are no more than two entries into any one container, package or administration container/device.
- Aseptic technique does not require more than 1 hour of continuous preparation.
- Aseptic technique is rigorously applied.

The following BUDs apply, with no requirement for additional sterility tests:

- Controlled room temperature: 1 hour
- Refrigerator: 1 hour
- Freezer: not applicable

Administration of the preparation must begin within 1 hour after the start of compounding; otherwise, the preparation must be discarded.

The container must always be correctly identified. In addition to mandatory information on the drug label, the BUD date and time should be included on the label.

6.1.5 Beyond-use times of 12 hours or less for preparations compounded in segregated areas

For compounded sterile preparations made in an LAFW that is not placed in an environment meeting the standards for ISO Class 7 air quality, or in a CAI that does not meet the requirements described in section 5.3.3.1, the following conditions must be met:

- The PEC is certified every 6 months and maintains ISO Class 5 air quality or better.
- Only low-risk preparations are compounded.
- Only one preparation is compounded at a time.
- The preparations are compounded in an area that is reserved for the compounding of sterile preparations and that minimizes contamination.
- The sink is not directly adjacent to the PEC and is separated from the immediate area of the PEC.
- The preparation area has no unsealed windows or doors leading to the exterior of the building. Furthermore, the preparation area is not in a high-traffic area or adjacent to construction sites, warehouses or food preparation sites.



- Personnel are fully compliant with procedures for hand and forearm hygiene, asepsis, garbing, and cleaning and disinfecting⁸⁶.

Given the risks associated with compounding sterile preparations under these conditions, administration of the preparation must begin within 12 hours after the start of compounding (Table 8); otherwise, the preparation must be discarded.

The container must always be correctly identified. In addition to mandatory information on the drug label, the BUD should be included on the label.

Table 8

| Summary of beyond-use dates (BUDs) for compounded sterile preparations prepared for immediate use or prepared in segregated compounding areas | | | |
|--|--|------------------------------|-------------------------|
| Type of preparation | BUDs for compounded sterile preparations without additional sterility test | | |
| | At controlled room temperature | With storage in refrigerator | With storage in freezer |
| Immediate-use preparation | 1 hour | 1 hour | NA |
| Preparation in LAFW (ISO Class 5 or better) in an environment where conditions do not meet ISO Class 7 standards or in CAI that does not meet requirements described in section 5.3.3.1 (segregated compounding areas) | 12 hours | 12 hours | NA |

CAI = compounding aseptic isolator; ISO = International Organization for Standardization; LAFW = laminar airflow workbench; NA = not applicable.

6.2 Compounded sterile preparation protocols

Protocols for compounded sterile preparations must include all of the information required to prepare the compound:

- name of preparation
- pharmaceutical form
- ingredients required
- quantity, concentration and source of ingredients
- necessary equipment
- compounding procedure
- storage method
- BUD
- references
- draft and revision date
- pharmacist's signature

⁸⁶ United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013. p. 365.



Appendix 7 presents a model for writing compounded sterile preparation protocols for each drug.

All protocols for pharmacy compounded sterile preparations must be stored together and must be readily available for quick consultation. The protocols must be reviewed and approved by the sterile compounding supervisor or delegate.

6.3 Compounded sterile preparation log

A compounded sterile preparation log must be completed during the compounding process.

The pharmacy must keep such a log for each individual patient, as well as a log for sterile preparations made in batches.

Computerized information and information recorded with cameras may be used as a record.

6.3.1 Compounded sterile preparation log for one patient (individual preparations)

The compounded sterile preparation log for an individual patient must contain the following information:

- patient's name
- prescription number (if compounded in a community pharmacy)
- patient's identification number (if compounded in a health care facility)
- preparation identification (official or assigned name, strength and dosage of the preparation)
- compounding procedure (master formulation record reference)
- for each ingredient (including primary and secondary diluents),
 - name
 - source
 - quantity/volume measured
 - batch number
 - drug identification number and lot number, as applicable
 - expiration date
- compounding date
- total quantity compounded
- preparation BUD
- identity of compounder and verifier at each stage of the process, as well as identity of the person who approved the preparation
- duplicate label, as described in the master formulation record
- description of final preparation
- results of quality control procedures (e.g., weight range of filled capsules, pH of aqueous liquids)
- documentation of any quality control issues and any adverse reactions or preparation problems



The log (paper-based or computerized) must be filed and retained for future reference as required by the relevant provincial/territorial regulatory authorities.

6.3.2 Compounded sterile preparation log for batch preparations

The compounded sterile preparation log for sterile preparations prepared in batches must contain the following information:

- preparation identification (official or assigned name, strength and dosage form of the preparation)
- compounding procedure (master formulation record reference):
 - equipment needed to prepare the preparation, as appropriate
 - mixing instructions, including order of mixing, mixing temperatures or other environmental controls, duration of mixing and other factors pertinent to replication of the preparation as compounded
- for each ingredient (including primary and secondary diluents),
 - name
 - source
 - quantity/volume measured
 - calculations needed to determine and verify quantities of ingredients and doses of active pharmaceutical ingredients
 - compatibility and stability information, including references when available
 - batch number
 - drug identification number and lot number, as applicable
 - expiration date
- compounding date
- total quantity compounded
- identity of compounder and verifier at each stage of the process, as well as identity of the person who approved the preparation
- description of the final preparation
- container used for dispensing
- sample labelling information, which shall contain, in addition to legally required information, generic name and quantity or concentration of each active ingredient, preparation BUD, storage conditions and prescription or control number (batch number), as applicable
- packaging and storage requirements
- results of quality control procedures (e.g., weight range of filled capsules, pH of aqueous liquids)

The log (paper-based or computerized) must be filed and retained for future reference as required by the relevant provincial/territorial regulatory authorities.



6.4 Patient file

For any compounded sterile preparation that has already been dispensed, all information required for review and assessment of the preparation by pharmacists and for subsequent treatment of the patient must be recorded in the patient file.

Information recorded in the patient file must allow users to accurately reproduce the prescribed preparation at a later date and identify the compounding personnel, if necessary.

The origin of the compounded sterile preparation dispensed to the patient must be recorded in the patient file in cases where the preparation was made by another pharmacy, as permitted by provincial/territorial legislation.

Any pharmacy (in the health care facility or the community) must be able to track information related to preparations that it dispenses, even if those preparations were made by another pharmacy.

6.5 Conduct of personnel in areas reserved for the compounding of sterile preparations

Personnel must behave in a professional manner, following all pertinent policies and procedures.

Regardless of which type of PEC is used for sterile compounding, all standards presented in section 6.5 apply.

6.5.1 Conditions that may affect preparation quality

Any of the following conditions will affect preparation quality⁸⁷. Personnel afflicted with any of these conditions shall be excluded from sterile compounding activities and sterile compounding areas until the condition has been remedied:

- uncontrolled weeping skin condition
- burns to the skin, including sunburns
- cold sores (active herpes simplex viral infection)
- conjunctivitis (viral or bacterial)
- active respiratory infection with coughing, sneezing or runny nose
- fresh piercings
- other fresh wounds

A person with permanent tattoos may compound sterile products. However, a recent tattoo on the face, neck or arms is considered a fresh skin wound, and the individual must cease sterile compounding activities and wait until the skin is completely healed before resuming such activities.

6.5.2 Conduct before entering the anteroom

Before entering the anteroom, personnel must⁸⁸

- remove personal outer garments (e.g., coat, hat, jacket, scarf, sweater, vest, boots and outdoor shoes);
- remove jewelry, studs and other accessories from fingers, wrists, forearms, face, tongue, ears and neck (this includes personal electronic devices or accessories, such as cell phone, iPod and earbuds, which are not permitted in the anteroom or clean room);

87 United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013. p. 376-7.

88 United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013. p. 376-7.



- remove all cosmetics, including makeup, false eyelashes, perfume, hair products such as hairspray, henna tattoos and paper tattoos, as these products can generate particles that are possible sources of contamination;
- tie up long hair;
- remove nail polish⁸⁹ and other nail applications (nail extensions and other synthetic nail-lengthening products are prohibited);
- ensure that natural nails are kept short and trimmed (0.6 cm);
- ensure that skin of hands and forearms is undamaged;
- change into dedicated, low-shedding apparel suitable for the controlled area (e.g., scrubs);
- wear pants that fully cover the legs;
- wear closed shoes and socks;
- wash hands.

6.5.3 Conduct in controlled areas (clean room and anteroom)

In controlled areas, the following measures should be taken.

- Food items, drinks, chewing gum, candy and cigarettes (or other smoking products) are prohibited⁹⁰.
- All access doors to controlled areas must be kept closed.
- Access to the controlled areas is restricted to personnel with specific responsibilities in the controlled areas.
- All personnel in the controlled areas must follow specified hand hygiene and garbing procedures.
- Only essential conversations are allowed, to minimize the risk of particulate contamination. Coughing, sneezing and talking in the direction of the LAFW should also be avoided.

6.6 Aseptic compounding of non-hazardous sterile preparations

6.6.1 General

The aseptic compounding process includes all activities related to completion of the final sterile preparation, including

- performing hand and forearm hygiene;
- garbing of personnel;
- disinfecting and introducing products and equipment into the clean room;
- disinfecting the PEC;
- disinfecting and introducing products and equipment into the PEC;
- using aseptic techniques to compound sterile preparations in the PEC;
- verifying, labelling and packaging final compounded sterile preparations.

89 Centers for Disease Control and Prevention. Guideline for hand hygiene in health-care settings. Recommendations of the Healthcare Infection Control Practices Advisory Committee and the HICPAC/SHEA/APIC/IDSA Hand Hygiene Task Force. *MMWR Morb Mortal Wkly Rep.* 2002;51(RR-16):1-48.

90 United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013. p. 379-80.



Personnel must develop work techniques to minimize the risk of cross-contamination and microbial contamination, to avoid errors and to maximize performance of the PEC. The pharmacist or pharmacy technician must apply professional judgment at all times.

The number of people in the clean room and anteroom must be limited to the minimum number required to perform aseptic compounding activities⁹¹.

Before the compounding of sterile preparations begins, the pharmacist or pharmacy technician must ensure that calculations are accurate and that the appropriate drugs, equipment and devices have been selected. The pharmacist or pharmacy technician must also ensure that compounding personnel follow the protocol for compounding the sterile preparation and must validate the preparations log.

Exposure of critical sites must be limited to a PEC that maintains ISO Class 5 air quality requirements.

6.6.2 Hand and forearm hygiene and garbing

Hand and forearm hygiene and garbing are the first important steps in preventing contamination of sterile products.

Hand and forearm hygiene is required for sterile compounding, regardless of the type of PEC that is used.

Hand and forearm hygiene is required for anyone entering the clean room.

6.6.2.1 Hand and forearm hygiene

After donning head and facial hair covers and face masks and dedicated shoes or shoe covers, personnel must wash and disinfect hands and forearms in the following sequence:

- Under warm running water, use a nail pick to remove debris from underneath fingernails.
- Wash hands and forearms up to the elbows with soap and water, for at least 30 seconds. Do not use brushes.
- Rinse with water.
- Dry hands and forearms with disposable, lint-free towel.
- Dispense ABHR with persistent activity onto one palm.
- Immerse fingertips of the other hand into the ABHR.
- Cover the forearm of the other hand with ABHR until the ABHR evaporates.
- Repeat with other hand and other forearm.
- Don gown.
- Enter the clean room.
- Dispense ABHR onto palm of one hand. Rub both hands with ABHR, making sure that all surfaces of the hands are covered. Continue to rub until the ABHR has evaporated.
- Allow hands to dry.
- Don sterile gloves. The gloves must cover the cuffs of the non-shedding gown.

91 United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD:USP; 2013. p. 379-80.



This hand-washing sequence must be documented in the policies and procedures and updated as appropriate⁹².

6.6.2.2 Garbing

PPE must be worn during sterile compounding, regardless of the type of PEC that is used.

Compounding personnel must don garb in the sequence described in the policies and procedures. The selected sequence must be documented and reviewed regularly⁹³.

The following general garbing order is recommended:

- While standing on the “dirty” side of the demarcation line in the anteroom, don hair net, then beard cover (if required) and then face mask.
- While stepping over the demarcation line, don shoe covers.
- Under warm running water, use a nail pick to remove debris from underneath fingernails, and then wash hands and forearms (up to the elbows) with warm water and soap for at least 30 seconds, rinse with warm water and dry with disposable, lint-free towel (*see* section 6.6.2.1).
- Apply ABHR with persistent activity.
- Don gown, closed at the neck and elastic cuffs.
- Apply ABHR with persistent activity to hands and allow hands to dry.
- Don sterile gloves and routinely disinfect them with sterile 70% isopropyl alcohol or equivalent agent during the compounding process.

Shoe covers or dedicated shoes are required at all times in the clean area of the anteroom and the clean room. All shoes must be closed, dry, clean and easy to maintain.

“Dedicated shoes” are reserved for walking in the “clean” area of the anteroom and the clean room and shall not be worn outside of the clean area of the anteroom. Dedicated shoes must be cleaned and disinfected once a week.

6.6.3 Introducing products and equipment into the clean room

Before any product is introduced into the anteroom, it must be removed from its cardboard shipping box. Cardboard has been found to harbour mould spores, so the product must then be wiped with a sporicidal agent. Any remaining packaging is left on the product and should not be removed until the product is introduced into the clean room from the anteroom. At this point, only packaging required for maintenance of sterility is retained.

Where packaging allows, compounding equipment and products must be disinfected with sterile 70% isopropyl alcohol just before being introduced into the clean room⁹⁴.

Non-shedding wipes or swabs must be used for disinfection. The wipes or swabs must be changed regularly during disinfection of equipment and products.

92 United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013. p. 376-7.

93 United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013. p. 376-7.

94 United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013. p. 376-7.



For introduction of compounding equipment and products into the clean room, the items must be placed in a plastic or stainless steel bin to help prevent errors (such as mixing up preparations for different patients or mixing two different batches). The bin is then placed in the pass-through for transfer to the clean room. Bins used for this purpose must be disinfected before use.

If there is no pass-through, the equipment and products are transferred from the “dirty” cart or bin to the “clean” cart or bin at the demarcation line in the anteroom and are then introduced into the clean room. The equipment and products are disinfected while being transferred to the clean cart or bin.

6.6.4 Cleaning and disinfecting the primary engineering control

Only compounding personnel who have successfully achieved the competencies required for sterile compounding may clean and disinfect ISO Class 5 environments, according to the following steps:

- Perform hand and forearm hygiene and garbing procedures.
- Disinfect the work surface of the PEC according to established procedures, ensuring the minimum frequency of disinfection as outlined in Table 9. If a different frequency of disinfection is to be followed, it should be established and justified by the results of air and surface sampling for viable particles.

Personnel must comply with the following requirements when cleaning and disinfecting the PEC:

- Disinfect non-powdered sterile gloves with sterile 70% isopropyl alcohol and allow to dry before starting to clean and disinfect the PEC.
- Avoid having the head and upper body enter the PEC.
- Use non-shedding, disposable wipes.
- Avoid contaminating the surface of wipes used for cleaning and disinfecting.
- Change wipes after disinfection of each section of the PEC.
- Clean and disinfect the PEC with clean wipes and germicidal disinfectant detergent, followed by sterile 70% isopropyl alcohol, at the start and end of the day or shift (minimum twice per day).
- Follow the cleaning method described in the pharmacy’s procedures.
- Follow the disinfecting method described in the pharmacy’s procedures (with regard to equipment, sequence and movements).
- Follow the manufacturer’s directions concerning dwell time for the disinfectant.
- Wait until the disinfectant has dried before compounding the first preparation in the PEC⁹⁵.
- Record cleaning and disinfecting activities in the maintenance log.

Sterile water shall be used for diluting concentrated disinfectant solutions used inside any ISO Class 5 device. The disinfectant should always be diluted according to the manufacturer’s instructions.

95 United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013. p. 391.



Table 9

| Minimum frequency and areas of the laminar airflow workbench (LAFW) to be cleaned and disinfected by compounding personnel* | | |
|---|--|--|
| Surface of LAFW | Frequency | Cleaning and disinfecting products† |
| All surfaces | <ul style="list-style-type: none"> - At the start of each workday - At the end of each workday | Germicidal disinfecting detergent, followed by sterile 70% isopropyl alcohol (minimum twice daily) |
| Work surface | <ul style="list-style-type: none"> - Before starting any sterile-product preparation - At each shift change - Whenever surface contamination is suspected - If there has been non-compliance with aseptic techniques | Sterile 70% isopropyl alcohol |
| Work surface and any surface that has been splashed | <ul style="list-style-type: none"> - When there is a spill | Sterile water for injection or irrigation (for cleaning), followed by sterile 70% isopropyl alcohol (for disinfecting) |
| All surfaces and subfloor | <ul style="list-style-type: none"> - Weekly (at the end of a workday) | Sterile water for injection or irrigation (for cleaning), followed by a sporicidal agent and then sterile 70% isopropyl alcohol (for disinfecting) |
| *Requirements are similar for cleaning and disinfecting a compounding aseptic isolator. | | |
| †Other products may be acceptable for disinfecting, if approved by the infectious disease department of the health care facility. | | |

6.6.5 Aseptic technique for compounding sterile preparations

Compounding personnel must use meticulous aseptic technique when preparing compounded sterile preparations. Compounding must occur in the critical area of the PEC, such that critical sites are exposed to first air. Each preparation must be completed from start to finish before compounding of another preparation is begun.

In the event of non-compliance with aseptic technique, the preparation must be discarded. In this situation, new supplies must be used, and the surface of the PEC must be disinfected before another preparation is started.

Gloved hands must be disinfected with sterile 70% isopropyl alcohol before re-introduction into the PEC or after gloves have come into contact with a microbiologically contaminated surface⁹⁶. If gloves are torn, they must be removed and hand and forearm hygiene performed before new gloves are donned. Even without tearing, gloves must be changed regularly. The frequency and circumstances of glove changes must be defined in a procedure.

Products and supplies must be intact, dry and unsoiled. Otherwise, the products and supplies must be discarded. All containers (e.g., bags of solution, vials and ampoules) must be examined before use. Products exhibiting turbidity, cloudiness or particulates must not be used.

All equipment with surfaces that can be disinfected must be disinfected with sterile 70% isopropyl alcohol before being introduced into the PEC. Non-shedding wipes or sterile swabs must be changed regularly during disinfection of equipment.

To reduce the risk of errors and to decrease turbulent air flow from the PEC, vials must not be allowed to accumulate in the PEC.

96 United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013. p. 379-80.



6.6.6 Verification of final compounded sterile preparations

6.6.6.1 Role of personnel in verification

The sterile compounding supervisor must perform the following activities:

- ensure that all compounded sterile preparations comply with compounding protocols;
- verify the identity of the ingredients (drug and diluent);
- verify the volume of the ingredients (drug and diluent);
- regularly verify the quality of the manipulations.

When compounding a preparation, compounding personnel must undertake the following activities:

- perform a visual inspection of each unit for evidence of particulates, to verify the clarity, colour and volume of the solution, to check the container for possible leaks and to verify the integrity of the container;
- verify the information on the label;
- place final compounded sterile preparations that require storage at 2°C to 8°C in the refrigerator pending verification and delivery to patients or the patient care unit (ice packs are suitable for maintaining the temperature of a cooled item but cannot be used for the cooling process; therefore, final compounded sterile preparations must be cooled in the refrigerator before being placed in a cooler).

6.6.6.2 Process for verification

Verification may be performed in one of three ways:

- direct observation during compounding;
- viewing of the identity and quantity of ingredients through an observation window located close to the PEC;
- remote observation using a digital camera connected to a monitor (*see* section 6.6.6.3 for additional detail).

6.6.6.3 Verification by image capture or live camera

Verification may be conducted by capturing images of the critical site (in the PEC) with a camera connected to a monitor. Such verification must be performed before the compounded sterile preparation is delivered to the patient. However, in this situation, if the verifying pharmacist or pharmacy technician notices that one or more procedures have not been followed correctly, all sterile preparations compounded during this period must be destroyed, and the destruction of preparations (because of non-compliance identified during verification) must be entered in the preparations log.

Appendix 8 gives examples of compounded sterile preparations that must be verified at each step of the compounding process.

6.6.6.4 Verification not required

Some preparations need not be verified during compounding because of the packaging or compounding preparation system used. As with all preparations, however, the equipment and products used must be verified before and after compounding. An additional verification method, by counting vials, ampoules and remaining material, shall be implemented.



Appendix 9 gives examples of compounded sterile preparations for which verification is not required during the compounding process.

6.6.6.5 Second verification

Each preparation must be inspected by a person other than the individual who performed the aseptic compounding. This person must inspect each unit for evidence of particulates, verify the clarity, colour and volume of the solution, check the container for possible leaks and verify its integrity⁹⁷.

Like the compounder, the verifier must sign the preparation log.

6.6.7 Labelling of final compounded sterile preparations

6.6.7.1 General

The sterile compounding supervisor must establish a policy for the labelling of compounded sterile preparations and ensure that it is followed.

The information on labels must follow federal/provincial/territorial legislation and regulations for drugs prepared or sold with or without a prescription. More specifically, the labels for compounded sterile preparations must meet the requirements of the applicable legislation and regulations.

All active ingredients must be identified on the label. The label must also include the concentration of each ingredient.

Each container for a compounded sterile preparation must be labelled.

A label must be affixed to each prepared unit, accompanied, if necessary, by a supplementary document (*see* section 6.6.7.2) to complete the required information.

Compounding personnel must label the following items:

- final compounded sterile preparations;
- each unit of a compounded sterile preparation for an individual patient, along with required auxiliary labels;
- each unit of sterile preparations compounded in batches (with, at a minimum, drug name, concentration, route of administration, batch number and BUD);
- each package containing final preparation units, along with auxiliary labels indicating required storage conditions and special precautions.

The compounding pharmacist or pharmacy technician must similarly label sterile preparations that have been compounded at the request of another pharmacy, where permitted by provincial/territorial legislation.

At the pharmacy where the compounded sterile preparations will be dispensed to the patient, another label must be added containing all information required by the respective provincial/territorial regulatory authority; a supplementary document must be prepared, if required. Both labels must be retained on the preparations.

97 United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013. p. 381.



6.6.7.2 Label and insert

The computer-generated self-adhesive label printed by the prescription and file management software may be too small to carry all relevant information to ensure safe, appropriate use of the compounded sterile preparation by the patient. In that situation, an insert must be prepared. The insert is considered to be an integral part of the label.

Together, the label and insert must provide all information required for proper use of the drug by the patient or for safe administration by a third party.

The label must contain the following information, at a minimum:

- pharmacy identification (name, address and telephone number of the compounder's or dispenser's pharmacy);
- drug identification (active ingredients, source, concentration, form, route of administration, volume, solute, amount prepared);
- overfill volume, when overfilling has occurred;
- special precautions (e.g., if product is an irritant);
- storage method;
- date when the sterile preparation was compounded;
- BUD;
- preparation batch number.

The package insert must include the following information:

- all information required by federal/provincial/territorial legislation and regulations regarding the labelling of medications that could not be included on the main label;
- details concerning mode of administration;
- special precautions related to drug storage (e.g., "Caution: contents must be refrigerated upon receipt — store between 2°C and 8°C. Do not freeze"; "Do not store medication in the refrigerator door"; "Keep out of reach of children");
- special precautions for disposal or destruction of the preparation;
- emergency contact information of the compounding pharmacy (where compounding has been undertaken by another pharmacy, as permitted by provincial/territorial legislation), provided there is explicit agreement on this matter between the two pharmacies involved.

6.7 Packaging

Appropriate packaging must be used for all preparations to be delivered to patients or other health care providers.

Preparations to be delivered must be packaged and labelled to ensure the safety of both the patient and the shipper.

6.7.1 Packaging process

During packaging, compounding personnel must

- put all final compounded sterile preparations in packaging that maintains each preparation's stability, integrity and storage conditions;



- place items with an attached needle in a second rigid container;
- indicate storage requirements on the final package (e.g., temperature, protection from light);
- indicate additional precautions on the final packaging (e.g., if product is an irritant);
- indicate transport precautions (e.g., temperature, fragility, safety) and instructions (name and address of patient) on the outside packaging of each item.

6.7.2 Packaging procedure

To maintain the integrity of compounded sterile preparations and the safety of patients and delivery personnel, the sterile compounding supervisor must develop and implement a packaging procedure for final compounded sterile preparations. Appendix 4 presents a model for writing such procedures. The packaging procedure must specify the following details:

- equipment to be used to prevent breakage, contamination, spills or degradation of the compounded sterile preparation during transport and to protect the carrier;
- equipment to be used to ensure that packaging protects compounded sterile preparations against freezing and excessive heat (for compounded sterile preparations requiring refrigeration, the packaging must maintain a temperature between 2°C and 8°C and for compounded sterile preparations to be kept at room temperature, the packaging must maintain a temperature between 19°C and 25°C);
- method to be used to confirm whether the temperature of compounded sterile preparations has been maintained during transport (e.g., temperature maintenance indicator, min/max thermometer, certified cooler);
- packaging to be used to protect against extreme temperatures (i.e., excessive heat or freezing) during transport of compounded sterile preparations, unless information is available demonstrating the product's stability at these temperatures.

6.8 Storage^{98, 99}

The sterile compounding supervisor must develop a storage procedure (*see* Appendix 4), and this procedure must be followed at all times.

All commercial products used for preparations must be stored immediately upon receipt. In addition, they must be handled and stored so as to prevent cross-contamination and incompatibilities.

Product storage conditions specified by the manufacturer must be strictly observed, regardless of where the products are stored (warehouse, pharmacy, delivery vehicle, loading dock, etc.).

For final compounded sterile preparations or products used for preparations, the storage temperature must be controlled and must remain within the limits specified in Appendix 10, regardless of the season.

Information on monitoring of room, refrigerator and other temperatures and controls related to implementation of the storage procedure must be recorded in the general maintenance log¹⁰⁰.

A biomedical refrigerator or freezer must be available for storing products, ingredients and final compounded sterile preparations that need to be refrigerated or frozen (*see* section 5.3.3.2).

98 United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013. p. 384.

99 United States Pharmacopeial Convention (USP). General chapter <1079>: good storage and shipping practices. In: *USP pharmacists' pharmacopeia*. Rockville, MD: USP; 2008–2009. p. 880.

100 United States Pharmacopeial Convention (USP). General chapter <1079>: good storage and shipping practices. In: *USP pharmacists' pharmacopeia*. Rockville, MD: USP; 2008–2009. p. 879.



Alternative storage must be provided when conditions are beyond acceptable temperature variations and when refrigerators and freezers are being cleaned.

Products that have been stored must be inspected before use for evidence of deterioration.

A procedure for verifying the BUDs of stored compounded sterile preparations and the expiration dates of commercial products must be developed and implemented to ensure that products and compounded sterile preparations that have become unusable are quickly discarded.

6.9 Transport and delivery of compounded sterile preparations

Policies and procedures must be developed and implemented for the transport of compounded sterile preparations and their delivery to patient care units, pharmacists and patients (*see* Appendix 4). A policy for return of expired or unused compounded sterile preparations from the patient's home or the patient care unit in a health care facility must also be developed.

The transport and delivery procedures must identify the delivery person and the times when the min/max thermometer must be checked during transport. The steps to be followed in the event of non-maintenance of target storage temperature during transport must be indicated in the procedure.

The transport and delivery procedures must include any precautions to be taken by the delivery person, especially during delivery (e.g., personal delivery of the compounded sterile preparation, rather than delegation to another person) and during return of medications, waste, and sharp or pointed items.

For community pharmacies and health care facility pharmacies making deliveries outside the facility, the delivery container should be lockable or sealed.

The sterile compounding supervisor must ensure that personnel involved in preparation and delivery of products (pharmacist, pharmacy technician, pharmacy assistant and driver) receive training on the transport and delivery procedures.

The pharmacist or pharmacy technician must dispose of any unused compounded sterile preparation returned from a patient's home.

In health care facilities, unused preparations returned from the patient care unit to the pharmacy may be reused if it can be shown that they have been properly stored (at the correct temperature, with protection from light, etc.) and there is no evidence of tampering¹⁰¹.

When a private carrier is used, the sterile compounding supervisor must verify the steps taken to ensure maintenance of the cold chain throughout transport and storage of compounded sterile preparations.

When a private carrier is to deliver compounded sterile preparations to a patient, the sterile compounding supervisor must ensure that the transport conditions will comply with the required storage conditions.

Where compounding is undertaken by another pharmacy, as permitted by provincial/territorial legislation, the compounding personnel must ensure that the preparation is transported to the dispensing pharmacy under conditions that maintain stability of the preparation. The receiving pharmacy must then ensure that transport conditions are maintained until the product is delivered to the patient.

101 United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013. p. 384-5.



6.10 Recall of sterile products or final compounded sterile preparations

When information obtained by a community or hospital pharmacy as a result of internal control, a complaint or a product recall shows that the grade or quality of a product or preparation does not meet requirements, the pharmacist or pharmacy technician must be able to

- identify patients who have received the compounded sterile preparation;
- notify patients or their caregivers that there is a problem with the preparation;
- perform the necessary follow-up if the preparation has been administered.

The information about individual units or batches of compounded sterile preparations recorded in the patient file and the preparation log must be sufficient to allow users to track recipients of compounded sterile preparations.

The sterile compounding supervisor must ensure that a procedure for recall of compounded sterile preparations has been developed and approved (*see* Appendix 4).

In health care facilities, the pharmacist or pharmacy technician must follow the established recall procedure, remove products already in circulation and follow up appropriately with patients likely to have used them.

The causes of the problem leading to the recall must be reviewed, and corrective and preventive measures must be identified and implemented, regardless of the location of the pharmacist's or pharmacy technician's practice.

6.11 Incident and accident management

When an incident or accident involving a compounded sterile preparation occurs, the compounding personnel must complete an event report and explanation form (*see* Appendix 11 for an example). In health care facilities or community pharmacies, a form developed or selected by the facility or pharmacy may be used.

Complaints, accidents, incidents and reported side effects must be evaluated to determine their cause, and the necessary steps must be taken to prevent re-occurrence. Each organization must have a process for this activity and must maintain a log. The information in the log is used to investigate deviations from protocol and to improve processes.

6.12 Waste management

In the performance of assigned duties, the pharmacist or pharmacy technician must^{102, 103}

- ensure that medications and sharp or pointed instruments are disposed of safely, in compliance with environmental protection laws in force in the jurisdiction;
- ensure that medications to be destroyed are safely stored in a location separate from other medications in inventory;
- develop and implement a procedure for destruction of pharmaceutical waste.

Pharmaceutical products that are expired or otherwise no longer usable are considered pharmaceutical waste.

102 National Association of Pharmacy Regulatory Authorities (NAPRA). *Model standards of practice for Canadian pharmacists*. Ottawa, ON: NAPRA; 2009. Available from: http://napra.ca/Content_Files/Files/Model_Standards_of_Prac_for_Cdn_Pharm_March09_Final_b.pdf

103 National Association of Pharmacy Regulatory Authorities (NAPRA). *Model standards of practice for Canadian pharmacy technicians*. Ottawa, ON: NAPRA; 2011. Available from: <http://napra.ca/pages/PharmacyTechnicians/pharmacytechniciansstandards.aspx>



7. QUALITY ASSURANCE PROGRAM

The sterile compounding supervisor must establish a quality assurance program to ensure the clear definition, application and verification of all activities that will affect the quality of compounded sterile preparations and the protection of personnel.

The quality assurance program is intended to generate information showing that the organization's personnel, facilities and equipment (PEC, etc.) attain and maintain the conditions required for contamination-free compounding of sterile preparations and that sterile preparations are being compounded in compliance with established procedures. This information is made available to and is used by personnel and other responsible individuals.

The verifications required by the quality assurance program help personnel to acquire data and identify trends, which in turn allow corrective and preventive actions to be taken, if necessary.

7.1 Program content

The quality assurance program must have four components:

1. verification of equipment, including the PEC;
2. verification of controlled areas (clean room and anteroom);
3. verification of aseptic compounding processes;
4. verification of final preparations.

Each component of the quality assurance program and its activities must be documented (*see* Appendix 12).

7.2 Results and action levels

For each of the specified components, the sterile compounding supervisor must establish a verification process, the results of which are assigned one of three levels:

- Compliance (no action required): mandatory specifications have been attained.
- Alert (tendency toward non-compliance): increased vigilance is required to prevent non-compliance.
- Action required (non-compliant): more in-depth investigation, immediate corrective action and/or preventive action are needed to avoid return to non-compliance.

7.3. Verification of equipment and facilities

7.3.1 Verification of equipment supporting compounding activities

7.3.1.1 Certification

Equipment that supports compounding activities, especially refrigerators, freezers, incubators and air sampling devices, must be certified with respect to its installation and operation and must be calibrated before being put into service and thereafter as recommended by the manufacturer.

A regular maintenance plan must be established, taking into account the manufacturer's recommendations for each device. If no manufacturer's recommendations are available, maintenance activities must be performed at least once a year by a qualified technician. The maintenance report must be saved in the general maintenance log.



7.3.1.2 Temperature readings

At least once a day, compounding personnel must check the temperature log of equipment with an integrated recording device (e.g., refrigerator, freezer, incubator), to review temperatures over the previous 24 hours, and must take corrective actions in case of substantial variance with respect to specified parameters.

When a thermometer is used as a verification instrument, the temperature must be read twice a day (at specified but different times of day; e.g., morning and night). The pharmacist or pharmacy technician must record and retain proof of calibration of the thermometer.

Temperature readings will include the actual temperature, the minimum temperature and the maximum temperature.

If a computerized temperature monitoring system is used, the system must offer features to record and store temperature readings at the same frequency as specified above (at a minimum). The system must also trigger an alarm if the temperature readings deviate from the acceptable range.

7.3.2 Verification of controlled rooms and the primary engineering control

7.3.2.1 Certification

The controlled areas of facilities and the PEC must be certified by a recognized organization

- at least every 6 months¹⁰⁴;
- during installation of new equipment or a new controlled area;
- during maintenance or repair of equipment (repair of PEC, ventilation system, etc.) or a controlled area (repair of hole in a wall, etc.) that might alter environmental or operational parameters;
- when investigation of a contamination problem or a problem involving non-compliance in the aseptic compounding process requires exclusion of malfunctioning facilities.

The program for monitoring facilities and the PEC must include a plan for sampling viable and non-viable particles.

7.3.2.2 Certificate provided by manufacturer (in factory)

The sterile compounding supervisor shall retain, for all HEPA filters and for the PEC, the manufacturers' certificates issued in the factory before delivery.

7.3.2.3 Environmental verification

An environmental verification program must be established to ensure that facilities maintain established specifications and uphold the quality and safety standards set by the industry.

Compliance with specifications for environmental parameters of facilities and proper operation of devices

The sterile compounding supervisor must ensure that all personnel on site

- have full knowledge of the measuring instruments used for verification;

¹⁰⁴ Occupational Safety and Health Administration (OSHA). *OSHA technical manual (OTM): controlling occupational exposure to hazardous drugs*. Section VI, Chapter 2. Washington, DC: US Department of Labor; 1999. Available from: https://www.osha.gov/dts/osta/otm/otm_vi/otm_vi_2.html



- know the specifications for each parameter being verified;
- know the procedure to be followed in case of non-compliance with respect to air pressure and temperature.

The temperature of ISO Class 7 and ISO Class 8 areas must be verified and documented at least once a day.

The differential pressure between controlled areas must be kept constant according to the specifications described in section 5.3.2.5 (*see* Tables 2, 3 and 4; Figure 1). Pressure must be measured continuously, and an alarm system must be in place to immediately advise personnel of non-compliance with specifications and to direct that action be taken, if necessary. A procedure must be developed to outline and explain the actions to be taken should the pressure differential deviate from specifications.

The indicators for proper operation of any device (LAFW, CAI, ACD, etc.) shall be monitored every day, and data shall be recorded in the general maintenance log.

Sampling of viable, non-viable and surface particles in controlled areas and the PEC¹⁰⁵

A written sampling plan for controlled areas and the PEC must be established.

Sampling plan

The plan for sampling air (for viable and non-viable particles) and surfaces must be established according to the specifications of a recognized standard, such as CETA application guide CAG-002, CAG-003 or CAG-008.

The air and surface sampling plan must include, for each controlled area (clean room and anteroom),

- sampling site diagram;
- type of sampling to be done;
- sampling methods to be used;
- number of samples to be obtained at each site;
- frequency of sampling;
- number of colony-forming units (CFUs) triggering action.

The sampling plan must allow for three types of samples:

- non-viable particles per cubic metre of air;
- viable particles per cubic metre of air;
- viable surface particles.

Sampling specifications

Samples must be obtained at least every 6 months from the air in controlled areas and in the PEC¹⁰⁶ *and* every time that the following conditions are present:

- during installation of new equipment or a new controlled area;

¹⁰⁵ United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013. pp. 373-5.

¹⁰⁶ United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013. pp. 373-5.



- during maintenance or repair of equipment (repair of PEC, ventilation system, etc.) or a controlled area (repair of hole in a wall);
- during investigation of a contamination problem or a problem involving non-compliance of personnel with aseptic processes.

Samples for determining the number of non-viable particles per cubic metre of air, viable particles per cubic metre of air and viable surface particles must always be obtained under dynamic operating conditions during each facility and PEC certification.

Sampling of non-viable particles in air

Non-viable particles in the air in controlled areas and the PEC must be sampled at least every 6 months¹⁰⁷ under dynamic operating conditions, as follows:

- by the qualified certifier, during certification of facilities;
- by employees of the community or health care facility pharmacy, provided the employees have been trained within the framework of an internal verification program (including training in use of a calibrated particle meter), to ensure proper operation of facilities and equipment.

The sterile compounding supervisor must ensure the competency of the certifier and the personnel chosen to conduct the sampling. Appendix 5 describes certification activities.

The values obtained must comply with the specifications established for each controlled area (ISO 14644-1 classification for air quality). See Table 1 for the classifications of air cleanliness by concentration of particles in controlled rooms and areas according to the ISO standard, and section 5.3.2 on the installation of areas reserved for activities related to the compounding of non-hazardous sterile preparations.

Calibration certificates for the equipment used to conduct the certification must accompany the report prepared after each certification.

The sterile compounding supervisor must ensure that the certification is performed in accordance with the most recent certification standards in force for the facilities and equipment used to compound sterile products.

Appendices 5 and 6 describe certification activities and the standards used by certifiers.

Sampling of viable particles in air and on surfaces

Sampling for viable particles must include

- sampling of viable particles per cubic metre of air for each established sampling site, using an air sampler (1000 L for ISO Class 5 and 500 L for all other areas);
- surface sampling of each established sampling site, whereby a 55-mm agar surface is used to gently touch the sample site, with a new agar plate being used for each sampling site (the agar will leave behind a residue, and the sampled area must be disinfected immediately after sampling).

¹⁰⁷ United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013. pp. 373-5.



The sampling of viable air and surface particles must be performed by a qualified individual such as a certifier or employees of the community or health care facility pharmacy. An established sampling procedure must be followed, and personnel must have received and successfully completed the proper training for this procedure.

The sterile compounding supervisor must

- obtain from the manufacturer a calibration certificate for the viable air sampler, to ensure that it can be regularly calibrated according to the manufacturer's recommendations and to allow appropriate training of personnel in its use;
- use the appropriate nutrient medium for plating of samples:
 - tryptic soy agar (low sulphur content) or soybean-casein digest medium for air samples
 - tryptic soy agar with lecithin and polysorbate for surface samples
 - for high-risk compounding, in addition to the above, malt extract agar or other media that support the growth of fungi
- verify the microbial proliferation capacity of each batch of nutrient medium used (the certificate for this test, provided by the manufacturer, must be retained¹⁰⁸).

The samples obtained must be either

- sent to a certified external laboratory; or
- incubated in the community or health care facility pharmacy, provided that
 - the incubator used is certified periodically;
 - procedures are in place for use and maintenance of the incubator and for surveillance of temperatures;
 - personnel are properly trained and are competent to read and interpret the results and to take appropriate preventive or corrective actions.

After sampling, the growth plates are recovered and taped. The plates are inverted and incubated¹⁰⁹. Tryptic soy agar should be incubated at 30°C to 35°C for 48 to 72 hours. Malt extract agar or other fungal media should be incubated at 26°C to 30°C for 5 to 7 days.

The contamination level at which corrective action is required will vary depending on the desired ISO air classification¹¹⁰. The following contamination levels require corrective action.

Volumetric sampling of facility air:

- Areas requiring ISO Class 5 air quality, threshold contamination > 1 CFU/m³ of air
- Areas requiring ISO Class 7 air quality, threshold contamination > 10 CFU/m³ of air
- Areas requiring ISO Class 8 air quality, threshold contamination > 100 CFU/m³ of air

108 United States Pharmacopeial Convention (USP). General chapter <51>: antimicrobial effectiveness. In: *USP pharmacists' pharmacopeia*. Rockville, MD: USP; 2008-2009.p. 706-8.

109 United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013. p. 375.

110 United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013. pp. 375, 379.



Surface sampling of PEC (direct contact, 55-mm agar plate):

- Areas requiring ISO Class 5 air quality, threshold contamination > 3 CFU/plate
- Areas requiring ISO Class 7 air quality, threshold contamination > 5 CFU/plate
- Areas requiring ISO Class 8 air quality, threshold contamination > 100 CFU/plate

During the first few months of sampling, the sterile compounding supervisor should ensure that samples are obtained more frequently than the minimum 6-month interval, to create a baseline for comparison.

If there is growth of any viable particles obtained via air sampling, surface sampling or GFS, the genus of the microorganism must be identified. Corrective and preventive actions (e.g., cleaning, disinfecting) will be based on this information.

The sterile compounding supervisor must analyze the data obtained and the trends observed with respect to the microbial load. If necessary, the sterile compounding supervisor should consult a microbiologist or infectious diseases specialist.

7.4 Quality assurance of personnel involved in aseptic compounding

The quality assurance program for the aseptic compounding process for personnel must include GFS and a media fill test, which are the two final steps of initial and periodic qualification of personnel, as mentioned in section 5.1.2.2.

7.4.1 Gloved fingertip sampling¹¹¹

GFS must include

- a sample obtained after sterile gloves are put on (after aseptic washing of hands and forearms) but before application of sterile 70% isopropyl alcohol (disinfecting gloves with sterile 70% isopropyl alcohol immediately before sampling would lead to “false negatives”);
- a sample obtained after the media fill test (described in section 7.4.2), making sure that the employee has not applied sterile 70% isopropyl alcohol to his or her gloves in the minutes before sampling.

Using tryptic soy agar contact plates with lecithin and polysorbate¹¹², the assessor obtains thumbprints and prints of gloved fingertips from both hands of the employee, asking the employee to gently press and roll each thumb and fingertip on the agar in the contact plate (one agar plate for each hand).

When the sampling is complete, the gloves must be taken off and thrown away, and hand and forearm hygiene must be performed.

The samples must be incubated between 30°C and 35°C and must be read within 48 to 72 hours.

For each employee, a negative result (0 CFU) must be obtained three times for the first GFS (obtained after sterile gloves are put on) before the employee can be permitted to compound sterile preparations.

For each employee, GFS after the media fill test must be completed annually for low- and medium-risk sterile compounding and every 6 months for high-risk sterile compounding. For this test, the total CFU count for both hands must be no more than 3 CFUs. If the result on any GFS after a media fill test is more than 3 CFUs, the sterile compounding supervisor is prompted to investigate the employee’s work practices, procedures, use of disinfectants, etc.

111 United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013. p. 378.

112 United States Pharmacopeial Convention (USP). General chapter <1116>: microbial evaluation of clean rooms and other controlled environments. In: *USP pharmacists’ pharmacopeia*. Rockville, MD: USP; 2008–2009. pp. 900-8.



7.4.2 Media fill test

The media fill test is a compounding simulation test conducted with nutrient media that promote bacterial growth. This test is used to verify the employee's performance of aseptic processing. For more information on this test, consult General Chapter <797> in the USP–NF¹¹³.

For the media fill test, the simulation chosen must be representative of activities performed under real compounding conditions in the particular environment and must represent the most complex preparations according to the microbiological risk level of preparations made there¹¹⁴.

A tryptic soy agar (low sulphur content) or soybean-casein digest nutrient medium must be used. For compounded sterile preparations with low or medium risk of microbial contamination, the nutrient medium must be sterile. For compounded sterile preparations with a high risk of microbial contamination, the nutrient medium must be non-sterile and must include simulation of sterilization by filtration.

The proliferation capacity of every batch of nutrient medium used must have been tested by the manufacturer, and the certificate for this test result must be retained by the compounding pharmacy¹¹⁵.

The containers used for media fill tests should be sent to a certified external laboratory or may be incubated in the pharmacy, provided the incubator is certified periodically and provided procedures are in place for use and maintenance of the incubator and for surveillance of required temperatures. In the latter situation, personnel must be properly trained to read the results.

The containers filled with nutrient medium for use in the media fill test must be incubated between 20°C and 25°C or between 30°C and 35°C for 14 consecutive days¹¹⁶. If two temperatures are used, the containers should be incubated for 7 consecutive days at each of the temperatures, starting with the higher temperature.

7.5 Quality assurance of compounded sterile preparations

The sterile compounding supervisor must establish a quality assurance program to ensure that preparations are compounded in compliance with established procedures.

The program must monitor, among other things,

- the presence of a compounding protocol for each compounded sterile preparation;
- compliance of the preparation with the prescription issued;
- compliance of labels affixed to containers with legislation and regulations;
- compliance with required documentation in the compounded sterile preparations log for individual patients and the batch compounded sterile preparations log, ensuring the performance of all verification steps required during and after compounding.

113 United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013. pp. 365-8.

114 United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013. pp. 365-8.

115 United States Pharmacopeial Convention (USP). General chapter <51>: antimicrobial effectiveness. In: *USP pharmacists' pharmacopeia*. Rockville, MD: USP; 2008–2009. pp. 706-8.

116 United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013. pp. 365-9.



7.6 Documentation of quality control activities

Written documentation related to the quality assurance program must be verified, analyzed and signed by the sterile compounding supervisor and retained for a period as designated by federal/provincial/territorial regulations.

The sterile compounding supervisor must

- investigate missing documentation, situations of non-compliance (where action is required) and deviations from protocols;
- identify trends concerning microbial load in controlled areas and types of microorganisms found;
- consult a microbiology specialist, if necessary;
- take corrective and preventive actions.

For the sampling of viable air and surface particles, the nutrient medium readings should be documented on a separate form for each type of sampling.

All completed documentation concerning components of environmental verification of controlled areas, the PEC and supporting equipment must be filed and retained with other compounding records, as per provincial/territorial pharmacy authorities.

Documents concerning purchase, organization and certification of the PEC must be accessible throughout the entire service life of the facility and the PEC.

All completed documentation concerning the quality assurance program for personnel involved in the aseptic compounding process (by GFS and media fill test), including nutrient medium readings, should be retained and made accessible.



8. SOURCE FOR ADDITIONAL INFORMATION

For more information on sterilization of high-risk compounds, depyrogenation by dry heat and the use of allergen extracts and radiopharmaceuticals as compounded sterile products, please refer to General Chapter <797> in the most recent edition of USP-NF.



9. GLOSSARY

| Term | Definition |
|------------------------------------|--|
| Accident | An action or situation in which the risk event occurs and has or could have an impact on the health status or well-being of the user (patient), personnel or a third party. An accident differs from an incident, which has no effect on the patient or any other person. |
| Anteroom | A room equipped with two doors, with a system/procedure that allows only one door to be open at any given time, which allows passage or movement of people or things from one environment to the other, while keeping the two environments isolated from one another. |
| Aseptic compounding process | All activities leading to completion of a final compounded sterile preparation, including hand and forearm hygiene, garbing, introduction of products and materials into the clean room, disinfection of the primary engineering control, use of aseptic techniques for compounding preparations in the primary engineering control, and verification and labelling of the compounded sterile preparations. The purpose of the process is to maintain the sterility of a preparation or drug compounded from sterile components. |
| Aseptic technique | Steps in the aseptic process, including all manipulations performed inside the primary engineering control by compounding personnel. |
| Assessment | Action of assessing and defining an employee's performance and competency. |
| Batch | Two or more units of a compounded sterile preparation that is intended to have uniform character and quality within specified limits, prepared in a single process and completed during the same limited period. |
| Beyond-use date (BUD) | Date and time after which a compounded sterile preparation cannot be used and must be discarded (because of a risk of loss of sterility). For the purposes of these Model Standards, administration of the compounded sterile preparation must begin before the BUD has passed ¹¹⁷ . |
| Cleaning | Removal of dirt, dust and other substances that may host microorganisms ¹¹⁸ . |
| Clean room | A room in which atmospheric properties (temperature, humidity, particle and microorganism content, pressure, airflow, etc.) are controlled. The room's functional parameters are kept at specified levels. The room is designed to minimize the introduction, generation and retention of particles. In the context of compounding non-hazardous sterile preparations, a clean room is an ISO Class 7 environment. For non-hazardous compounding, the clean room has positive pressure relative to adjacent areas. For hazardous compounding, the clean room has negative pressure relative to adjacent areas. |
| Commercial container | Container holding a commercially manufactured drug or sterile nutrient, the consumption and sale of which are authorized in Canada; if the drug or sterile nutrient is authorized by Health Canada's Special Access Programme, such consumption and sale may be limited. |
| Competencies | Significant job-related knowledge, skills, abilities, attitudes and judgments required for competent performance of duties by members of a profession. |
| Compounding | The act of preparing a pharmaceutical preparation, through preliminary work, to put it into a usable state. The term "compound" also refers to the material that has been prepared (e.g., a chemical or pharmaceutical preparation). |
| Compounding aseptic isolator (CAI) | Isolator used specifically for compounding non-hazardous sterile preparations and designed to ensure an aseptic environment during the transfer of material and drugs and during the performance of aseptic technique. The CAI is designed to prevent any exchange between the air inside the clean room and the air within the isolator, unless the air is first filtered by a high-efficiency particulate air filter. |
| Compounding personnel | Pharmacists, pharmacy technicians and/or pharmacy assistants assigned to the compounding of sterile preparations. |

117 United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013.

118 United States Pharmacopeial Convention (USP). General chapter <1072>: disinfectants and antisepsis. In: *USP pharmacists' pharmacopeia*. Rockville, MD: USP; 2008–2009.

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| Compounding pharmacist or pharmacy technician | Pharmacist or pharmacy technician who compounds or supervises the compounding of sterile preparations according to prescriptions issued to the pharmacy where the pharmacist or pharmacy technician works or for a dispensing pharmacist who has requested this service (where the compounding is undertaken by another pharmacy, as permitted by provincial/territorial legislation). |
| Compounding procedure | Procedure that describes all steps to be followed in the compounding of sterile preparations and performed according to a particular packaging method (e.g., syringe filled for intravenous use, elastomeric preparation). |
| Compounding protocol | Protocol that describes all steps to be followed in the compounding of a specific sterile preparation, with which the compounder must comply. The protocol must include all of the information to be recorded in the preparation log. |
| Containment | Arrangement of equipment to contain the particles of hazardous products within the chosen space. |
| Contiguous | A term describing a location or space that adjoins another. Example: The clean room is contiguous with the anteroom and the surrounding pharmacy areas. Synonyms: adjacent, adjoining, bordering, abutting, surrounding, neighbouring |
| Controlled area or room | An area or space where the only activities taking place are those related to the compounding of sterile preparations. In such locations, to confirm whether air quality meets the requirements of the specified ISO class, the concentrations of viable and non-viable particles suspended in the air are verified according to a sampling plan. Corrective measures are taken when necessary to meet the ISO class requirements ¹¹⁹ . The clean room and anteroom are examples of controlled areas. Also known as a classified area or room. |
| Critical area | Work area inside a primary engineering control ensuring ISO Class 5 air, in which personnel compound sterile preparations and where critical sites are exposed to unidirectional airflow from a high-efficiency particulate air filter. |
| Critical site | Any surface likely to come into contact with a sterile drug or liquid (e.g., vial septa, injection sites) or any exposed opening (open vials, needle hubs) and likely to be in direct contact with the ambient air, with air filtered by means of a high-efficiency particulate air filter or with humidity (oral secretions or mucous membranes) or likely to be contaminated by touch ¹²⁰ . |
| Detergent | Product that eliminates accumulated dirt from a solid medium by resuspension or dissolution. |
| Disinfectant | A disinfecting agent, typically of a chemical nature, that can destroy microorganisms or other pathogens, but not necessarily bacterial spores or fungal spores. Refers to substances applied to inanimate objects ¹²¹ . |
| Disinfection | Treatment that eliminates most of the pathogens present on an object or surface ¹²² . |
| Dispensing (of a prescription) | All activities related to the validation (including therapeutic appropriateness), preparation and packaging of a patient's medication prepared pursuant to a prescription. |
| Facilities | All devices, rooms and spaces that are organized, arranged and modified to ensure suitability for the activities to be conducted therein. In the context of sterile compounding, facilities include the clean room and the anteroom. |
| Final sterile preparation | A sterile preparation that has been prepared according to a preparation-specific compounding protocol, that respects the prescribing physician's prescription and that is ready to be stored and then administered to a patient. |
| First air | The air exiting the high-efficiency particulate air filter in a unidirectional air stream that is essentially particle free. |

119 United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013.

120 United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013.

121 United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013.

122 United States Pharmacopeial Convention (USP). General chapter <1072>: disinfectants and antisepsis. In: *USP pharmacists' pharmacopeia*. Rockville, MD: USP; 2008–2009.



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| Gloved fingertip sampling (GFS) | Method of assessing whether an employee is meeting the standards for aseptic technique. Using tryptic soy agar contact plates with lecithin and polysorbate, the assessor obtains thumbprints and prints of gloved fingertips from both hands of the employee, asking the employee to gently press and roll each thumb and fingertip on the agar in the contact plate (one agar plate for each hand) ¹²³ . The agar plates are then incubated and the colony-forming units counted. |
| Hand hygiene | All methods related to hand washing performed with soap and water, followed by a waterless, alcohol-based hand rub with persistent activity. |
| Hazardous drug | A drug for which research on humans or animals has shown that any exposure to the substance has the potential to cause cancer, lead to a developmental or reproductive toxic effect or damage organs ¹²⁴ . Such drugs are considered hazardous because their effects present risks for personnel ¹²⁵ . |
| Hazardous material | A material that, because of its properties, constitutes a danger to an employee's health, safety or physical integrity ¹²⁶ . Hazardous materials are dangerous products regulated by a workplace hazardous material information system; as such, they are considered "controlled" products under the <i>Controlled Products Regulations</i> ¹²⁷ . |
| Hazardous product | Substances that entail risks for personnel because of their effects. For the purposes of these Model Standards, the term "hazardous product" refers to both hazardous drugs and hazardous materials, depending on the situation. |
| Incident | An action or situation that has no impact on the health status or well-being of the user (patient), personnel or a third party, but that does have an unusual result that could, on other occasions, lead to consequences. An incident differs from an accident, which has or could have an impact on the patient or another person ¹²⁸ . |
| Incubator | A device used in microbiology to keep cultures at a constant temperature. |
| Insert | Document or leaflet containing information about a drug additional to that written on the computer-generated label produced by the prescription management software; provides the patient with information as required by regulations. |
| Label (for identifying a sterile preparation) | Label that identifies drugs prepared or sold with or without a prescription. It is usually computer-generated and usually has an adhesive backing. It must bear the information that is required by federal/provincial/territorial regulations. |
| Laminar airflow workbench (LAFW) | A device that provides an ISO Class 5 environment for the exposure of critical sites when sterile preparations are being compounded. The airflow is unidirectional (laminar flow), and the first air (air exiting the high-efficiency particulate air filter ¹²⁹) is free from airborne particulates. |
| Laminar flow hood | See "Laminar airflow workbench" |
| Log | Book or notebook in which data are recorded or compiled to demonstrate that the quality of the pharmacy aseptic compounding process has been maintained. A log may be in computerized format. |
| Maintenance of competency | Continued ability to integrate and apply knowledge, know-how, judgment and personal qualities necessary to practise in a safe and ethical fashion in a designated role and framework ¹³⁰ . |
| Maintenance (of facilities and equipment) | Operations for maintaining the proper functioning of facilities or equipment according to established specifications or for re-establishing the satisfactory operational condition of facilities, including the heating, ventilation and air conditioning system and related equipment. |

123 United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013.

124 National Institute for Occupational Safety and Health (NIOSH). NIOSH alert: preventing occupational exposures to antineoplastic and other hazardous drugs in health care settings. Publ. No. 2004-165. Atlanta, GA: Department of Health and Human Services, Centers for Disease Control and Prevention, NIOSH; 2004 Sep. Available from: <http://www.cdc.gov/niosh/docs/2004-165/pdfs/2004-165.pdf>

125 Association paritaire pour la santé et la sécurité du travail du secteur affaires sociales (ASSTSAS). *Prevention guide — safe handling of hazardous drugs*. Montréal, QC: ASSTSAS; 2008. Available from: <https://www.irsst.qc.ca/media/documents/PubIRSST/CG-002.pdf>

126 Association paritaire pour la santé et la sécurité du travail du secteur affaires sociales (ASSTSAS). *Prevention guide — safe handling of hazardous drugs*. Montréal, QC: ASSTSAS; 2008. Available from: <https://www.irsst.qc.ca/media/documents/PubIRSST/CG-002.pdf>

127 *Controlled Products Regulations*, SOR/88-66, 1987. Available from: <http://laws-lois.justice.gc.ca/eng/regulations/SOR-88-66/>

128 Commission de la santé et de la sécurité du travail (CSST). *Material safety data sheet user's guide*. CSST; 2010. Available from: <http://www.reptox.csst.qc.ca/Documents/SIMDUT/GuideAng/Htm/GuideAng.htm>.

129 United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013.

130 Canadian Nurses Association. *Joint position statement: Promoting continuing competence for registered nurses*. Ottawa, ON: The Association; 2004. Available from: http://www.nurses.ab.ca/content/dam/carna/pdfs/DocumentList/EndorsedPublications/PS77_promoting_competence_e.pdf



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| Material safety data sheet (MSDS) | A “document that provides information on a controlled product, namely its toxic effects, the protective measures for avoiding overexposure or chemical hazards, and the procedures to follow in an emergency. The supplier sends the MSDS to the employer when the product is sold. It must be kept on the premises by the employer in a location known by personnel, and be easily and rapidly accessible to those who are likely to come in contact with the product ¹³¹ . The employer should have it before a product is used for the first time”. |
| Media fill test | Test used to qualify aseptic techniques of compounding personnel and the organization’s ability to produce preparations that are “sterile.” For this test, a nutrient medium replaces the actual product during performance of the aseptic technique ^{132,133} . |
| Multiple-dose container | Commercial drug container in multiple-dose format for parenteral administration only. The product usually contains an antimicrobial preservative ¹³⁴ . |
| Personal protective equipment (PPE) | All garb and accessories, such as mask, gloves, gown and safety goggles, that protect both the sterile preparation and the personnel. It enables compliance with the expected specifications of a controlled environment and protects personnel from exposure to physical or chemical risks ^{135, 136} . |
| Pharmacist | Registrant in good standing with one of the pharmacy regulatory authorities in Canada. |
| Pharmacy assistant | Person who has earned a vocational school diploma for completing a pharmacy assistant course or any person who has received proper training that is deemed equivalent. |
| Pharmacy bulk vial | Commercial container for parenteral sterile preparations intended for packaging that contains several individual doses. Such packaging is used only by pharmacies with an intravenous admixture program. During the final packaging, in several doses, the pharmacy bulk vial must be perforated with a transfer device only once, by introducing a needle or transfer “spike.” |
| Pharmacy technician | Person who has earned a college degree or diploma from an accredited pharmacy technician program, has passed the national examination and has been licensed or authorized by a provincial/territorial health professional regulatory authority to practise as a pharmacy technician. |
| Policy | All the general principles adopted by a private or public organization for conducting its activities. By extension, the term “policy” also refers to the text or document presenting these principles. |
| Primary engineering control (PEC) | A device that provides an ISO Class 5 environment for the exposure of critical sites during aseptic compounding. For compounding of non-hazardous sterile preparations, PECs include laminar airflow workbenches and compounding aseptic isolators. For compounding of hazardous sterile preparations, a containment primary engineering control (C-PEC), such as a biological safety cabinet or compounding aseptic containment isolator, must be used ¹³⁷ . |
| Procedure | All steps to be taken, the means to be used and the methods to be followed in performing a task. |
| Protocol | Document describing in detail all steps to be followed or behaviours to be adopted in specific clinical circumstances. |
| Repack/repacking | The process of packing again or the action of repacking (“reprocessing”). Examples include making 12-tablet packages from a pack (bottle) of 100 tablets and filling 1-mL syringes from a 10-mL pack (vial). |

131 Commission de la santé et de la sécurité du travail (CSST). *Material safety data sheet user’s guide*. CSST; 2010. Available from: <http://www.reptox.csst.qc.ca/Documents/SIMDUT/GuideAng/Htm/GuideAng.htm>

132 United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013.

133 Health Canada, Health Products and Food Branch Inspectorate. *Good manufacturing practices (GMP) guidelines – 2009 edition, Version 2* (GUI-0001). Ottawa, ON: Health Canada; 2009, revised 2011 Mar 4. p. 85. Available from: <http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui-0001-eng.php>

134 United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013.

135 Association paritaire pour la santé et la sécurité du travail du secteur affaires sociales (ASSTSAS). *Prevention guide — safe handling of hazardous drugs*. Montréal, QC: ASSTSAS; 2008. Available from: <https://www.irsst.qc.ca/media/documents/PubIRSST/CG-002.pdf>

136 National Institute for Occupational Safety and Health (NIOSH). NIOSH alert: preventing occupational exposures to antineoplastic and other hazardous drugs in health care settings. Publ. No. 2004-165. Atlanta, GA: Department of Health and Human Services, Centers for Disease Control and Prevention, NIOSH; 2004 Sep. Available from: <http://www.cdc.gov/niosh/docs/2004-165/pdfs/2004-165.pdf>

137 United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013. p. 263.



| | |
|--------------------------------|---|
| Single-dose vial | Single-dose commercial container corresponding to a fixed dose of a drug intended for parenteral administration only ¹³⁸ . Labeled as such by the manufacturer. |
| Stability (period of) | Period of time during which a properly compounded sterile preparation maintains, within specified limits and throughout the storage and usage period, the properties and characteristics that it had when it was compounded. |
| Sterile compounding supervisor | A person assigned by the head of the pharmacy department of a health care facility or by the pharmacy owner or manager to supervise, organize or oversee all activities related to the compounding of sterile preparations. |
| Sterilization by filtration | Use of a sterilizing-grade membrane to produce a sterile final solution, where a sterilizing-grade membrane is a membrane approved for filtering 100% of a <i>Brevundimonas (Pseudomonas) diminuta</i> culture to a concentration of 10 ⁷ colony-forming units/cm ² of filtering surface and to a minimum pressure of 30 psi; depending on the manufacturer, the nominal size of the membrane pores is 0.22 µm or 0.2 µm ¹³⁹ . |
| Third-party evaluator | A pharmacist or pharmacy technician with expertise in sterile preparation compounding, at arm's length from the facility/pharmacy and free of any real or perceived conflict of interest with the individual being evaluated. |
| Training | Acquisition of a totality of theoretical, technical and practical knowledge concerning pharmacy preparation. |
| Unidirectional airflow | Airflow moving in a single direction in a robust and uniform manner and at sufficient speed to reproducibly sweep particles away from the critical site. |

138 United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013.

139 United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013.



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11. APPENDICES

APPENDIX 1 POLICIES AND PROCEDURES FOR THE COMPOUNDING OF NON-HAZARDOUS STERILE PREPARATIONS

| NON-HAZARDOUS STERILE PREPARATIONS | | | |
|------------------------------------|---|--|---|
| Policy # | Topic | | ✓ |
| A | PERSONNEL AND FACILITIES | | |
| 1. | Obligations of personnel | | |
| 1.1 | Attire and dress code (e.g., personal clothing, jewelry, makeup, hairstyles) | | |
| 1.2 | Health conditions (reasons for temporary withdrawal from compounding activities) | | |
| 1.3 | Expected behaviour in controlled areas (e.g., no drinking, eating or other activities not related to compounding; expectation that procedures will be followed; avoidance of unnecessary conversations) | | |
| 2. | Training and assessment of personnel | | |
| 2.1 | Initial training and assessment program | | |
| 2.2 | Program to assess maintenance of competency | | |
| 2.3 | Training and assessment of cleaning and disinfecting personnel | | |
| 3. | Delegation of activities | | |
| 3.1 | Delegation of technical activities to persons other than pharmacists or pharmacy technicians | | |
| 4. | Facilities and equipment | | |
| 4.1 | Access to controlled areas | | |
| 4.2 | Necessary facilities and equipment | | |
| 4.3 | Maintenance of facilities and equipment (e.g., certification of rooms and devices, calibration, maintenance of pre-filters and high-efficiency particulate air filters, verification of pressure) | | |
| 4.4 | Cleaning and disinfecting activities for facilities and equipment | | |
| B | COMPOUNDED STERILE PREPARATIONS | | |
| 1. | Bringing equipment and products into the clean room and primary engineering control | | |
| 2. | Determining beyond-use dates of products used in a preparation | | |
| 3. | Determining beyond-use dates of final preparations | | |
| 4. | Hand and forearm hygiene | | |
| 5. | Garbing in compounding areas and for compounding | | |
| 6. | Cleaning and disinfecting the primary engineering control | | |
| 7. | Aseptic techniques (with details for each of the techniques used) | | |
| 8. | Verification of the compounding process (including validation of calculations by a pharmacist) and of final preparations | | |
| 9. | Labelling of final preparations | | |
| 10. | Packaging of final preparations | | |
| 11. | Preparation of injectable products outside regular operating hours of the compounding department of a health care facility | | |
| 12. | Storage of products used and final preparations | | |
| 13. | Transport and delivery of final preparations (to the patient, to patient care units or to the dispensing pharmacist) | | |
| 14. | Recording of preparations in the patient file | | |

| | | | |
|----------|-----|---|--|
| | 15. | Biomedical waste management (e.g., at the pharmacy, returns from patients or patient care units, instructions to patients) | |
| | 16. | Recall of sterile products or compounded sterile preparations | |
| C | | QUALITY ASSURANCE PROGRAM | |
| | 1. | Verification and maintenance of equipment | |
| | 2. | Environmental control of facilities and primary engineering control (e.g., pressure verification, air and surface sampling plan) | |
| | 3. | Quality assurance of aseptic process for personnel (e.g., gloved fingertip sampling, media fill tests) | |
| | 4. | Quality assurance of compounded sterile preparations (e.g., existence of a protocol, compliance with prescription, documentation in logs) | |



APPENDIX 2 MANDATORY AND SUPPLEMENTAL REFERENCES

Compounding personnel must be able to consult a wide variety of up-to-date references in the pharmacy at any time.

A. Mandatory references

At a minimum, the sterile compounding supervisor must make available a recent edition of the following publications:

- Standards, guidelines and policies of the relevant pharmacy regulatory authority
- Trissel LA. *Handbook on injectable drugs*. Bethesda, MD: American Society of Health-System Pharmacists.
- United States Pharmacopeial Convention (USP). *USP pharmacists' pharmacopeia*. Rockville, MD: USP; current version (contains all USP chapters useful to pharmacists, including General Chapter <797>: Pharmaceutical Compounding – Sterile Preparations).

B. Supplemental references

1. GENERAL TEXTS ON STERILE PREPARATIONS

Book

- Buchanan EC, Schneider PJ. *Compounding sterile preparations*. 3rd ed. Bethesda, MD: American Society of Health-System Pharmacists; 2009. 496 pages.

Periodicals

- *American Journal of Health-System Pharmacists*. Available from: <http://www.ajhp.org>
- *Canadian Journal of Hospital Pharmacy*. Available from: <http://www.cjhp-online.ca/index.php/cjhp>
- *International Journal of Pharmaceutical Compounding*. Available from: <http://www.ijpc.com>

Websites: associations and agencies

- ASHP Sterile Compounding Resource Center: <http://www.ashp.org/compounding>
- Pharmacy Compounding Accreditation Board, a service of the Accreditation Commission for Health Care: <http://achc.org/pcab>
- Critical Point, LLC: <http://www.criticalpoint.info/>

2. REFERENCE TEXTS: PHYSICAL-CHEMICAL STABILITY, COMPATIBILITY AND STABILITY

- *Compendium of pharmaceuticals and specialties*. Ottawa, ON: Canadian Pharmacists Association. Updated yearly.
- King JC. *King guide to parenteral admixtures* [electronic version]. Napa, CA: King Guide Publications Inc. Updated quarterly.
- Trissel LA. *Trissel's 2 clinical pharmaceuticals database (parenteral compatibility)* [electronic database]. Truven Health Analytics Inc. Updated regularly.

3. REFERENCE TEXT: PHARMACOKINETICS

- Spruill WJ, Wade WE, DiPiro JT, Blouin RA, Pruemmer JM. *Concepts in clinical pharmacokinetics*. 6th ed. Bethesda, MD: American Society of Health-System Pharmacists; 2014. 264 pages.



APPENDIX 3 TRAINING OF COMPOUNDING PERSONNEL AND CLEANING AND DISINFECTING PERSONNEL

A. Training of compounding personnel

| # | ELEMENTS TO COVER IN TRAINING | | | |
|------|---|----|----|----|
| 1. | FOR THE COMPOUNDING OF NON-HAZARDOUS STERILE PREPARATIONS | PH | PT | PA |
| 1.1 | Know the relevant federal/provincial/territorial legislation and regulations related to pharmacy compounding, as well as other governing standards, guides or guidelines. | X | X | |
| 1.2 | Know and apply all policies and procedures related to the pharmacy compounding of sterile preparations, especially those related to hand hygiene, garbing, aseptic techniques, airflow principle, facilities (ISO Classes 5, 7 and 8), material, equipment, behaviour of personnel in compounding rooms, forms and logs to be completed, labelling, storage, distribution to patients, quality controls (sampling) and maintenance and disinfecting of sterile-preparation compounding areas. | X | X | X |
| 1.3 | Know physical and chemical properties, such as stability, physical-chemical compatibility and incompatibility, osmolality and osmolarity. | X | | |
| 1.4 | Know pharmaceutical and medical abbreviations. | X | X | X |
| 1.5 | Know and understand the importance of particulate and microbial contamination. | X | X | X |
| 1.6 | Perform pharmacy sterile-product compounding tasks meticulously, precisely and competently. | X | X | X |
| 1.7 | Know and apply appropriate aseptic techniques in the workplace. | X | X | X |
| 1.8 | Know the operation and correct use of equipment, materials and automated devices available for the sterile preparations to be compounded. Know how to calibrate the devices used. | X | X | X |
| 1.9 | Be able to recognize errors in the compounding technique of compounding personnel. | X | X | |
| 1.10 | Have a good command of the pharmaceutical calculations required to compound sterile preparations. | X | X | X |
| 1.11 | Understand the importance of and apply accurate measurements. | X | X | X |
| 1.12 | Apply disinfection measures for sterile-preparation compounding rooms, facilities and materials. | X | X | X |
| 1.13 | Know the data to be monitored in controlled areas (temperature, pressure, humidity) and document the data in the appropriate logs. Know and apply the corrective measures to be applied when irregularities are identified. | X | X | X |
| 1.14 | Know how the primary engineering control and secondary ventilation system (heating, ventilation and air conditioning system) operate. Know, apply or enforce appropriate corrective measures when an irregularity is identified. | X | X | X |
| 1.15 | Know and apply quality assurance measures for the various compounded sterile preparations. | X | X | |
| 1.16 | Know and follow the verification process. | X | X | X |
| 1.17 | Know and use the incident/accident documentation logs. | X | X | X |
| 1.18 | Know drug delivery systems. | X | X | X |
| 1.19 | Know and establish levels of risk and beyond-use dates. | X | | |
| 1.20 | Know and, if applicable, perform additional sterility testing. | X | X | |
| | | | | |



| | | | | |
|-----|---|---|---|---|
| 2. | FOR THE COMPOUNDING OF HIGH-RISK NON-HAZARDOUS STERILE PREPARATIONS (MADE WITH NON-STERILE PRODUCTS) | | | |
| 2.1 | Have the competency required to compound sterile preparations. | X | X | X |
| 2.2 | Know and correctly perform sterilization by filtration. | X | X | X |
| 2.3 | Know and correctly perform the filter integrity verification. | X | X | X |
| 2.4 | Know and correctly perform the bacterial endotoxin test. | X | | |

B. Training of cleaning and disinfecting personnel

| # | ELEMENTS TO COVER IN TRAINING | PH/PT | PA | C&D |
|--|--|-------|----|-----|
| 1. | FOR CLEANING AND DISINFECTING THE GENERAL AREA FOR COMPOUNDING OF NON-HAZARDOUS STERILE PREPARATIONS | | | |
| 1.1 | Know all policies and procedures related to cleaning and disinfecting the equipment, furniture and facilities, notably those related to hygiene and asepsis, personal protective equipment, and cleaning and disinfecting tasks. | X | X | X |
| 1.2 | Know and don the correct garb. | X | X | X |
| 1.3 | Know and correctly perform hand hygiene. | X | X | X |
| 1.4 | Know, correctly perform and document cleaning and disinfecting tasks for the general area for compounding of non-hazardous sterile preparations. | X | X | X |
| | | | | |
| PH = pharmacist; PT = pharmacy technician; PA = pharmacy assistant; C&D = cleaning and disinfecting personnel. | | | | |



APPENDIX 4 PROCEDURE TEMPLATE

| | |
|---|--|
| Pharmacy name: Or Hospital XYZ pharmacy department: | Procedure # _____ Revised: <input type="checkbox"/> Yes <input type="checkbox"/> No Approved by _____ Date <i>(dd/mm/yyyy)</i> _____ Effective date: _____ <i>(dd/mm/yyyy)</i> |
| Procedure title: | |
| Aim and objective: ➤ Describe the objective of the procedure. | |
| Target personnel: Use this section to describe the expected responsibilities for each group that will be affected by this procedure. <input type="checkbox"/> Sterile compounding supervisor <input type="checkbox"/> Pharmacist <input type="checkbox"/> Pharmacy technician <input type="checkbox"/> Pharmacy assistant <input type="checkbox"/> Cleaning and disinfecting personnel <input type="checkbox"/> Other: _____ | |
| Required facilities, equipment and material: Include the following types of information here: ➤ Facilities and equipment required to apply the procedure. ➤ Materials (e.g., devices, instruments) required to apply the procedure. ➤ Products to be used. ➤ Containers to be used. ➤ Logs to be used or completed. | |
| Procedures Describe in detail what must be done by each person affected by the procedure, for each step or part of the procedure. Include examples of labels, symbols, logs, etc., that are to be used. Attach relevant documents, such as contracts, copies of legislation or regulations, manufacturers' instruction manuals, copies of administrative decisions and other related procedures. | |
| List of logs and assessment of competencies required for this procedure: 1. 2. | |
| References: Indicate here the references used to draft the procedure, with relevant publication dates and edition numbers, to facilitate successive updates. | |



| | |
|---|------------------------------------|
| Procedure history: | |
| Procedure # _____ | |
| Drafted by: _____, pharmacist | Date: _____ <i>(dd/mm/yyyy)</i> |
| Revised by: _____, pharmacist | Date: _____ <i>(dd/mm/yyyy)</i> |
| Revision: <input type="checkbox"/> Full <input type="checkbox"/> Partial Amended version: <input type="checkbox"/> Yes <input type="checkbox"/> No | |
| Change made: | |
| Revised by: _____, pharmacist | Date: _____ <i>(dd/mm/yyyy)</i> |
| Revision: <input type="checkbox"/> Full <input type="checkbox"/> Partial Amended version: <input type="checkbox"/> Yes <input type="checkbox"/> No | |
| Change made: | |



APPENDIX 5 MINIMUM INDICATORS FOR CERTIFICATION OF CONTROLLED AREAS AND PRIMARY ENGINEERING CONTROL

Note: The following appendix lists the responsibilities of the certifier, a person engaged to certify sterile-product compounding rooms and the primary engineering control (PEC). This information is provided here for the benefit of the sterile compounding supervisor, to allow assessment of the services provided during certification of areas and equipment in each respective pharmacy.

| 1. Before certification visit | |
|---|--|
| <ul style="list-style-type: none"> ▪ Ideally meets the client (sterile compounding supervisor) to discuss the certification process; during the meeting, the certifier <ul style="list-style-type: none"> ➤ asks whether problems have occurred since the last certification; ➤ asks whether there are any concerns about the operation of rooms or devices (e.g., PEC). ▪ Knows the PPE required to enter a controlled room and the garbing sequence. ▪ Knows the required procedure for hand and forearm hygiene before putting on gloves and entering a controlled room. | |
| 2. General precertification requirements | |
| <ul style="list-style-type: none"> ▪ Cleans and disinfects all equipment brought into the controlled rooms. ▪ Performs certification of the controlled rooms and PEC following the steps and methods recommended by the applicable standards. ▪ Uses the applicable standards for certification (see Appendix 6). ▪ Uses the devices required by the standards (see Appendix 6). ▪ Uses calibrated devices that are in good condition. ▪ Knows the standards to be used for certification and knows how to apply them. ▪ Wears the appropriate PPE to enter and work in the compounding rooms for hazardous and non-hazardous sterile preparations. ▪ Performs the work meticulously and professionally. | |
| 3. Certification steps, directed by CETA application guides | |
| 3.1 Certification of controlled areas | |
| <ul style="list-style-type: none"> ▪ Uses the criteria of CETA application guides CAG-002 and CAG-008 for certification of the clean room. ▪ Performs a count of non-viable particles. ▪ Measures the volume of air supply or the velocity for each HEPA filter in the room. ▪ If the air volume for HEPA filters cannot be measured, measures the air velocity profile for each terminal or line HEPA filter (as applicable) in the controlled room. ▪ If the velocity profile is measured, calculates the air volume for the HEPA filter. ▪ Verifies the integrity of the HEPA filter with a photometer. ▪ Verifies temperature. ▪ Verifies humidity. ▪ Verifies sound (noise) level.* ▪ Verifies light level.* ▪ Verifies the behaviour of the room and its equipment using smoke tests. ▪ Ensures that the doors to each room are fully closed when measuring pressure differentials between rooms. ▪ Obtains the dimensions of the room and its total volume of air supply, to allow calculation of number of air changes per hour. <p>* Note: The frequency of certain verifications, such as sound and light levels, may vary depending on needs and agreements.</p> | |



| | |
|---|--|
| 3.2 Certification of BSC | |
| <ul style="list-style-type: none"> ▪ Certifies the BSC according to CETA application guides CAG-003 and CAG-005. ▪ Takes readings to measure the velocity of the air supply of the BSC according to CETA application guides CAG-003 and CAG-005. ▪ Performs a count of non-viable particles. ▪ Verifies the count of non-viable particles 0.5 µm in diameter. ▪ Verifies the count of non-viable particles in at-rest (optional) and in-operation (dynamic) states, measured at five reading points, with a minimum of two 1-minute, 1 m³ samples per reading point (the acceptable limit is 3520 particles). | |
| 3.3 Certification of LAFW | |
| <ul style="list-style-type: none"> ▪ Certifies the LAFW in accordance with CETA application guide CAG-003. ▪ Measures the velocity of the LAFW air supply by taking a minimum of eight readings in the centre of every 30 cm², at a distance 30 cm from the surface of the HEPA filter or protective screen. ▪ Performs a count of non-viable particles. ▪ Verifies the count of non-viable particles 0.5 µm in diameter. ▪ Verifies the count of non-viable particles in at-rest (optional) and in-operation (dynamic) states, measured at five reading points, with a minimum of two 1-minute, 1 m³ samples per reading point (the acceptable limit is 3520 particles). ▪ Recommends that LAFW pre-filters be changed, if required. | |
| 3.4 Certification of CAI and CACI | |
| <ul style="list-style-type: none"> ▪ Certifies devices according to the manufacturer's recommendations, referring to CETA application guide CAG-002-2006 (Compounding Isolator Testing Guide). ▪ Performs the following certifications using all tests required by CETA application guide CAG-002-2006): <ul style="list-style-type: none"> ➤ Airflow test ➤ Verification of internal pressure ➤ Verification of installation site ➤ Verification of HEPA filter ➤ Containment integrity and enclosure leak test ➤ Recovery time test ➤ Smoke test ➤ Test of preparation entry and output ➤ Count of non-viable particles | |
| 4. After certification | |
| <ul style="list-style-type: none"> ▪ Answers questions and requests from the sterile compounding supervisor related to the certification and its procedure. ▪ Does the required quick cleaning of rooms and devices. ▪ Verifies that all certification labels are correctly printed and affixed. ▪ Provides the sterile compounding supervisor with a preliminary report, in writing (recommended but not mandatory) or, at a minimum, verbally. ▪ Submits a final certification report that includes all information required by pharmacy regulatory authorities to confirm certification. ▪ Submits recent calibration certificates for the devices used in the certification (attached to the final certification report). | |

BSC = biological safety cabinet; CACI = compounding aseptic containment isolator; CAI = compounding aseptic isolator; CAG = CETA application guide; CETA = Controlled Environment Testing Association; HEPA = high-efficiency particulate air; LAFW = laminar airflow workbench; PEC = primary engineering control; PPE = personal protective equipment.



APPENDIX 6 CERTIFICATION OF CONTROLLED AREAS, LAMINAR AIRFLOW WORKBENCHES AND BIOLOGICAL SAFETY CABINETS

| TARGET | CERTIFICATION STANDARDS | CERTIFICATIONS |
|---|--|--|
| <p>Laminar airflow workbench (LAFW)</p> <p>(vertical or horizontal laminar flow hoods)</p> | <ul style="list-style-type: none"> • CETA CAG-003 • IEST-RP-CC-002.3: Unidirectional-Flow, Clean-Air Devices • IEST-RP-CC-034-2 • ISO 14644-1 | <p>LAFW certification includes steps carried out:</p> <p><u>In accordance with CETA CAG-003:</u></p> <ul style="list-style-type: none"> • Airflow velocity testing • HEPA filter leak test • Induction leak/back streaming test • Airflow smoke pattern test • Particle count survey <p><u>Equipment used:</u></p> <ul style="list-style-type: none"> • Particle counter • Thermal anemometer • Smoke machine • Photometer |
| <p>Biological safety cabinet (BSC), Class II, type B2</p> <p>(For certification of other types of BSC, please refer to the standards.)</p> | <ul style="list-style-type: none"> • CETA CAG-003 and CETA CAG-005 • NSF Standard 49-2012: Biological Safety Cabinetry: Design, Construction, Performance and Field Certification • ISO 14644-1 | <p>Class II, type B2 BSC certification includes steps carried out:</p> <p><u>In accordance with CETA CAG-003 and CETA CAG-005:</u></p> <ul style="list-style-type: none"> • Measurement of air supply profile • Measurement of air intake velocity • Smoke test • HEPA filter integrity test • Verification that interlock system (between discharge probe and air supply motor) is working properly (for Class II, type B2 BSC) • Verification of device calibration (less than 20% air loss in 15 seconds) (for Class II, type B2 BSC) • Count of non-viable particles (0.5 µm) in operational (dynamic) state; at-rest state is optional <p><u>Equipment used:</u></p> <ul style="list-style-type: none"> • Particle counter • Thermal anemometer • Smoke machine and aerosol generator • Photometer • Direct volume measurement device |



| | | |
|--|---|--|
| <p>Compounding aseptic isolator</p> | <ul style="list-style-type: none"> • CETA CAG-002-2006: Compounding Isolator Testing Guide | <p><u>In accordance with CETA CAG-002-2006:</u></p> <p><u>All tests required by CETA, for example:</u></p> <ul style="list-style-type: none"> • Airflow test • Verification of internal pressure • Verification of installation site • Verification of HEPA filter • Containment integrity and enclosure leak test • Recovery time test • Smoke test |
| <p>Compounding aseptic containment isolator</p> | <ul style="list-style-type: none"> • CETA CAG-002-2006: Compounding Isolator Testing Guide | <ul style="list-style-type: none"> • Test of preparation entry and output • Count of non-viable particles <p><u>Equipment used:</u></p> <ul style="list-style-type: none"> • Thermal anemometer • Pressure measurement device (in inches of water or pascals) • Tools for adjusting alarms • Smoke machine • Photometer • Particle counter (small) • Aerosol generator • Chronometer |



| | | |
|---|---|---|
| <p>Clean room for the compounding of sterile preparations and controlled areas</p> | <ul style="list-style-type: none"> • CETA CAG-003: Certification Guide for Sterile Compounding Facilities • NEBB Procedural Standards for Certified Testing of Clean rooms • IEST-RP-CC-006.3: Testing Clean Rooms • ISO 14644-1 (section on number of particles, particle counters, and sampling plan and methods) | <p><u>Certification of controlled areas and rooms includes the following steps in accordance with CETA CAG-003:</u></p> <ul style="list-style-type: none"> • Count of non-viable particles in operational (dynamic) state (ISO 14644-1) • Certification of HEPA filter (IEST-RP-CC-006.3) • Verification of terminal or line HEPA filter • Measurement of pressure differential between controlled rooms • Verification of air changes per hour (by measuring volumes of air or room velocity) • Verification of behaviour of rooms and equipment using smoke tests • Verification of temperature • Verification of relative humidity • Measurement of luminosity • Measurement of noise level (sound) <p><u>Equipment used:</u></p> <ul style="list-style-type: none"> • Particle counter • Tripod for the room • Tripod for the LAFW or BSC • 0.3-µm filter (for cleaning) • “Tent” to capture air volume • Thermal anemometer • Smoke machine • Photometer • Pressure measurement device (in inches of water or pascals) • Thermometer • Hygrometer • Light meter • Sound level meter |
|---|---|---|

CAG = CETA application guide; CETA = Controlled Environment Testing Association; HEPA = high-efficiency particulate air; IEST = Institute of Environmental Sciences and Technology; ISO = International Organization for Standardization; NEBB = National Environmental Balancing Bureau.

Note: Some certifying technicians have credentials from certain US agencies (e.g., NSF International, NEBB, CETA). These credentials, obtained from the agencies in question after appropriate training, indicate that the holder has sound knowledge of the standard and how it must be applied and verified.

Information on certifiers can be found on the following websites: <http://www.nsf.org> (select the following options: “Regulatory resources” and then “NSF certification”) and <http://www.nebb.org> (select “NEBB Certified firm/professional/chapter” and then search by “NEBB certified professional”).



APPENDIX 7 TEMPLATE FOR THE DRAFTING OF COMPOUNDING PROTOCOLS TO BE COMPLETED FOR EACH DRUG

| | | | |
|--|--|-----------------------------|--|
| Name of compounded product: | Protocol number and version (e.g., 001-01) | | |
| Concentration: | Effective date: (dd/mm/yyyy) | | |
| Pharmaceutical form: | Authorized by: _____, pharmacist | | |
| Route of administration: | | | |
| FORMULA | | | |
| Ingredients | Quantities | Physical description | Other information (e.g., DIN, Lot number) |
| | | | |
| Additional information about the ingredients: | | | |
| Include any additional pertinent information about the ingredients required for compounding. | | | |
| Indicate any specific precautions to be taken when handling the ingredients. | | | |
| Notes on calculations and measurements: | | | |
| Indicate any characteristics of the calculations, measurements or ingredient preparation that must be done before the specific procedure is carried out. | | | |
| Indicate any requirement for verification by the pharmacist. | | | |
| Examples: | | | |
| <ul style="list-style-type: none"> - Quality control of devices to be carried out and documented before measurements are taken. - Accuracy of measurement devices. - Verification and documentation of ingredients, batch numbers and beyond-use dates. - Type of report required on the compounding form. | | | |
| Required devices, instruments and materials | | | |
| Indicate all materials and equipment that will be required to compound the sterile preparations. | | | |
| Compounding method | | | |
| Describe all steps of the sterile-product compounding process. | | | |



Quality control

Specify the procedure for determining the lot number of the final compounded sterile preparation.

Specify all quality control procedures that are to be carried out during compounding and documented by the pharmacist and/or pharmacy technician.

Specify all quality control procedures that are to be carried out by the pharmacist on the final compounded sterile preparation. Indicate the expected specifications.

| Example Quality control | Expected specification |
|-------------------------------|--|
| Appearance of the preparation | Clear, colourless solution with no visible particles |
| | |

Packaging

Describe the type of packaging in which the final compounded sterile preparation will be presented to the patient.

Stability and storage

Specify the preservation requirements of the compounded sterile preparation.

Specify the shelf life of the compounded sterile preparation (beyond-use date).

Indicate the references used to determine shelf life.

Labelling

Indicate mandatory information that must be on the label of the compounded sterile preparation.

A) When kept at the pharmacy or sent to another pharmacy

B) When dispensed to a patient

Sample label

Name of preparation:

Date when preparation was made:

Lot:

Quantity prepared:

Beyond-use date:

Shelf life:

Verified by:

Customer label

In addition to the legally mandated information, add:

- lot number of compounded sterile preparation
- beyond-use date
- precautions and other patient information leaflet



| | |
|--|--|
| <p>Training</p> <p>Indicate the training that personnel must undergo before the specific sterile compounding procedure is implemented.</p> | |
| <p>References consulted:</p> <p>Indicate the source of the specific sterile compounding procedure. Indicate any documentation supporting the stability of the final compounded sterile preparation.</p> | |
| <p>Preparation data sheet history No.:</p> | |
| <p>Date drafted: <i>(dd/mm/yyyy)</i></p> | <p>Drafted by:</p> |
| <p>Revised: <i>(dd/mm/yyyy)</i></p> <p>Change made:</p> | <p>Revised by:</p> <p>Version number changed: <input type="checkbox"/> YES <input type="checkbox"/> NO</p> |
| <p>Revised: <i>(dd/mm/yyyy)</i></p> <p>Change made:</p> | <p>Revised by:</p> <p>Version number changed: <input type="checkbox"/> YES <input type="checkbox"/> NO</p> |



APPENDIX 8 EXAMPLES OF STERILE PREPARATIONS THAT MUST BE VERIFIED AT EACH STAGE OF COMPOUNDING

| Packaging or system used | Examples |
|--|---|
| Ophthalmic drops | 50 mg/mL vancomycin ophthalmic solution prepared from a 500-mg vial. The vehicle used and product taken from the vial must be checked before insertion into the dispenser bottle. |
| Diluted cassette | 50 mg/mL Morphine-HP® in a 10-mL vial diluted to a final concentration of 10 mg/mL for subcutaneous infusion. The volume of morphine and the volume of diluent must be checked before they are put into the cassette. |
| Preparation made using a volumetric pump (e.g., Baxa-Repeater®, PharmAssist) | Verification of the pump setting each time the volume is changed, more frequently if necessary (e.g., if a large number of units is prepared). |



APPENDIX 9 EXAMPLES OF STERILE PREPARATIONS THAT DO NOT REQUIRE VERIFICATION DURING THE COMPOUNDING PROCESS

| Packaging or system used | Examples |
|--|---|
| Syringe filled with a single product | Syringe of 300 µg filgrastim for subcutaneous administration three times per week, prepared from a 300 µg/mL vial of filgrastim |
| ADD-Vantage™ or Mini-Bag Plus type system | 500 mg Primaxin® IV every 6 hours, prepared using the ADD-Vantage™ system (http://www.hospira.com/Products/addvantagesystem.aspx) or vial compatible with a Mini-Bag Plus |
| Contents of vial (powder) to be injected into a bag, minibag, Intermate or other container, when the entire contents of the vial will be used | 1 g cefazolin IV every 8 hours Dose prepared using a 1-g vial of powder diluted in 50 mL of 0.9% NaCl |
| Morphine or hydromorphone cassette, when starting with the product at the same concentration (at this point, it is the concentration per millilitre that is important, so the number of empty vials must be counted) | Cassette of morphine at a concentration of 5 mg/mL for subcutaneous administration, prepared from 30 mL vials of 5 mg/mL morphine (undiluted) |



APPENDIX 10 TEMPERATURES FOR DIFFERENT TYPES OF STORAGE

| Storage type | Temperature range |
|-------------------------------|-------------------|
| Freezing | -25°C to -10°C* |
| Refrigeration (cold) | 2°C to 8°C* |
| Refrigeration (cool) | 8°C to 15°C* |
| Controlled room temperature | 15°C to 20°C† |
| Drug conservation temperature | 15°C to 30°C |

*United States Pharmacopeial Convention (USP). General notices and requirements. In: *USP pharmacists' pharmacopeia*. Rockville, MD: USP; 2008. p. 29.

†United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013.



APPENDIX 11 INCIDENT/ACCIDENT REPORTING AND FOLLOW-UP FORM

Note: This is an example of a form that pharmacists and pharmacy technicians should have in place.

| Incident/accident* reporting and follow-up | | | |
|---|---|--|---|
| Reporting an incident <input type="checkbox"/> accident <input type="checkbox"/> | | | |
| General information | | | |
| Date and time of incident/accident: | Reported by: | | |
| Name of patient affected, if applicable: | Full address: | | |
| | Phone number: | | |
| Pharmacy personnel involved: | | | |
| Information about incident/accident | | | |
| (Summary of the situation and consequences) | | | |
| Disclosed to the patient concerned: <input type="checkbox"/> | | | |
| Name of pharmacist responsible for follow-up: | | | |
| Analysis of causes | | | |
| Causes: (Identify causes of the problem) | Options for corrections or changes: (Assess potential corrections or changes to be made) | Corrections or changes chosen: (Indicate the corrections or changes to be made) | |
| Action plan | | | |
| Actions (Describe the actions to be taken and the steps required to correct the situation, with a specific timeline. Determine who will be responsible for implementation.) | Responsible | Deadline | ✓ |
| Monitoring | | | |
| Verifications (To ensure that the corrections and changes are effective and fully implemented.) | Responsible | | ✓ |
| Closing of the file | | | |
| Pharmacist responsible for follow-up: (signature) | | Date file closed: | |

*An accident is an action or situation in which the risk event occurs and has or could have an impact on the health status or well-being of the user (patient), personnel or a third party. An incident is an action or situation that has no impact on the health status or well-being of the user (patient), personnel or any third party, but that does have an unusual result that could, on other occasions, lead to consequences.



APPENDIX 12 COMPONENTS OF A QUALITY ASSURANCE PROGRAM

| COMPONENT | CONTROLS | FREQUENCY |
|-------------------|--|--|
| FACILITIES | Certification of clean rooms and anteroom | <ul style="list-style-type: none"> • Every 6 months • When the controlled area is installed • When new equipment is installed • When rooms or equipment are repaired or maintained • When a contamination problem is identified • When investigation of a contamination problem or non-compliance in the aseptic preparation process requires exclusion of malfunctioning facilities |
| | Sampling of controlled areas under operational (dynamic) conditions: <ul style="list-style-type: none"> - Viable and non-viable particles, air and surfaces - According to a sampling plan | <ul style="list-style-type: none"> • Every 6 months (more frequently at the start of the quality assurance program) • When the controlled area is installed • When new equipment is installed • When the controlled area or equipment is repaired or maintained (e.g., when high-efficiency particulate air filter changed) • When a contamination problem is identified • When investigation of a contamination problem or non-compliance in the aseptic preparation process requires exclusion of malfunctioning facilities • According to an internal verification program |
| | Verification of temperature and humidity in controlled areas | <ul style="list-style-type: none"> • Once a day |
| | Pressure differential between controlled areas | <ul style="list-style-type: none"> • Continuous reading and notification system to prevent non-compliance • Periodic verification (once a week) by the sterile compounding supervisor • Notification system (in the absence of a continuous reading system, assign personnel to verify and record the pressure differential twice a day) |
| EQUIPMENT | | |
| | Certification of PECs | <ul style="list-style-type: none"> • Before first use • Every 6 months • When a new PEC is installed • When the PEC is repaired or maintained • When a contamination problem is identified • When investigation of a contamination problem or non-compliance in the aseptic preparation process requires exclusion of malfunctioning equipment |
| | Temperature verification (e.g., refrigerator, freezer, incubator) | <ul style="list-style-type: none"> • Once a day (if unit has a built-in reading device) • Twice a day (if unit has no built-in reading device) |
| | Operational indicators of PECs and other devices used (e.g., automated compounding device) | <ul style="list-style-type: none"> • Verified daily before use • Verified continuously by personnel |



| | | |
|---|---|---|
| | <p>Sampling of PECs under operational (dynamic) conditions:</p> <ul style="list-style-type: none"> - Viable and non-viable particles, air and surfaces - According to a sampling plan | <ul style="list-style-type: none"> • Every 6 months (more frequently at the start of the quality assurance program) • When a new PEC is installed • When the PEC is repaired or maintained • When a contamination problem is identified • When investigation of a contamination problem or non-compliance in the aseptic preparation process requires exclusion of malfunctioning equipment • According to an internal verification program |
| PERSONNEL | Competency assessment | <ul style="list-style-type: none"> • At initial qualification: theoretical and practical aspects • At periodic qualifications: theoretical and practical aspects • When assessing incidents and accidents • When a contamination problem is identified |
| | Gloved fingertip sampling | <ul style="list-style-type: none"> • At initial qualification: theoretical and practical aspects • Once a year for low- and medium-risk compounding • Every 6 months for high-risk compounding • When assessing incidents and accidents • When a contamination problem is identified |
| | Media fill tests | <ul style="list-style-type: none"> • At initial qualification: theoretical and practical aspects • Once a year for low- and medium-risk compounding • Every 6 months for high-risk compounding • When assessing incidents and accidents • When a contamination problem is identified |
| FINAL COMPOUNDED STERILE PREPARATION | Verification of compounding protocols (usage and maintenance) | <ul style="list-style-type: none"> • In accordance with the quality assurance program |
| | Verification that preparation matches prescription | <ul style="list-style-type: none"> • In accordance with the quality assurance program |
| | Verification of label compliance | <ul style="list-style-type: none"> • In accordance with the quality assurance program |
| | Entry in logs | <ul style="list-style-type: none"> • In accordance with the quality assurance program |
| PEC = primary engineering control. | | |



12. BIBLIOGRAPHY

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