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MODEL STANDARDS FOR PHARMACY COMPOUNDING OF 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 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 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. Requirements of the Chapter <800> of the United States Pharmacopeia-National Formulary (USP-NF) were also taken into consideration in the preparation of the new NAPRA Model Standards. 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 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–pharmacist–patient 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 therapy, e.g., for patients with burns)
- radiopharmaceuticals

Pursuant to these Model Standards, sterility is also required for 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	Name
ABHR	Alcohol-based hand rub
ACD	Automated compounding device
ACPH	Air changes per hour
ASSTSAS	Association paritaire pour la santé et la sécurité du travail du secteur affaires sociales, a joint sector-based association dedicated to occupational health and safety in the health and social services sector in the province of Quebec
BSC	Biological safety cabinet
BUD	Beyond-use date
CACI	Compounding aseptic containment isolator
CETA	Controlled Environment Testing Association
CFU	Colony-forming unit
C-PEC	Containment primary engineering control
GFS	Gloved fingertip sampling
HEPA	High-efficiency particulate air
HVAC	Heating, ventilation and air conditioning
ISO	International Organization for Standardization
NF	National Formulary (United States)
NIOSH	National Institute for Occupational Safety and Health (United States)
PPE	Personal protective equipment
USP	United States Pharmacopeia



5. CORE REQUIREMENTS FOR A STERILE COMPOUNDING SERVICE

In addition to strict aseptic techniques, the compounding of hazardous sterile preparations requires safety measures to protect personnel and the environment.

Hazardous products can penetrate the body through the skin, by ingestion, by accidental injection (needle-stick injury) or by inhalation. According to some studies, absorption through the skin is the primary known route of penetration⁸.

Absorption through the skin occurs by direct contact with contaminated surfaces or objects. Penetration by ingestion occurs by eating foods that have been contaminated or by putting contaminated hands or objects, particularly pens, into the mouth^{9, 10}. Inhalation of vapourized drugs can also be a source of contamination¹¹.

References on the safe handling of hazardous products must be consulted before compounding services for such products can be offered. Additional laws and regulations governing the compounding of hazardous sterile preparations and other hazardous materials may exist at the federal/provincial/territorial level, and these must also be consulted.

5.1 Personnel

5.1.1 Roles and responsibilities

5.1.1.1 Pharmacy manager¹² or pharmacy department head¹³

The pharmacy manager or pharmacy department head is responsible for developing, organizing and supervising all activities related to pharmacy compounding of hazardous 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 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.

In the pharmacy of a health care facility, a hazardous drugs committee¹⁴ should be established. The committee should comprise representatives of the employer, representatives of compounding and administration personnel, and representatives of cleaning and disinfecting personnel for the compounding areas. A pharmacist or pharmacy technician must be designated to support hazardous products management.

8 American Society of Health-System Pharmacists. ASHP guidelines on handling hazardous drugs. *Am J Health Syst Pharm.* 2006;63(12):1172-93.

9 American Society of Health-System Pharmacists. ASHP guidelines on handling hazardous drugs. *Am J Health Syst Pharm.* 2006;63(12):1172-93.

10 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>

11 American Society of Health-System Pharmacists. ASHP guidelines on handling hazardous drugs. *Am J Health Syst Pharm.* 2006;63(12):1172-93.

12 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.

13 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.

14 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>

5.1.1.2 Sterile compounding supervisor

Definition

A pharmacist or pharmacy technician designated to supervise activities related to the compounding of 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 the compounding of hazardous sterile preparations. 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 training¹⁵, 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).
- Prevention measures are implemented, in collaboration with the pharmacy manager or pharmacy department head, to limit exposure of personnel to hazardous products.
- The facilities and equipment used to compound hazardous 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 hazardous 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.

¹⁵ Please consult the relevant provincial/territorial pharmacy regulatory authority for training requirements defined in each jurisdiction.



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 training¹⁶, 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 hazardous sterile preparations;
- enforce or ensure compliance with required rules relating to asepsis, hygiene, cleanliness and safety;
- 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;

¹⁶ Please consult the relevant provincial/territorial pharmacy regulatory authority for training requirements defined in each jurisdiction.



- 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 hazardous 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 care¹⁷.

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 training¹⁸. 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.

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 and with chemical contamination of the environment. Stringent work methods^{19,20} 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 hazardous sterile preparations must have the appropriate mix of

17 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

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

19 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.

20 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.



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.

Before compounding any hazardous sterile preparations, employees must receive specific training in the workplace and must undergo and pass an assessment of their competency, as described in section 5.1.2.3. An annual competency assessment program must also be put into place.

All personnel (pharmacists, pharmacy technicians and pharmacy assistants) must know and apply safe-handling procedures for the receipt, storage, distribution and disposal of hazardous products and hazardous waste, as well as the procedures for dealing with accidental exposure and spills.

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

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

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 used for compounding hazardous sterile preparations (*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 the compounding of hazardous sterile preparations.

Any cleaning and disinfecting employee who has successfully completed theoretical and practical training in the workplace may perform cleaning duties in facilities where hazardous sterile preparations are compounded, 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 hazardous 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 area for compounding hazardous sterile preparations.

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 the compounding of hazardous sterile preparations, at arm's length from the facility/pharmacy and free of any real or perceived conflict of interest 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, the aseptic compounding process, and accidental exposure and spills (*see* Appendix 3);
- a practical test in the workplace clean room (including GFS and a media fill test, with



simulations involving a hazardous product) 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 hazardous 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 the compounding of hazardous sterile preparations

- 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 demonstrate the 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 hazardous 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 hazardous sterile preparations must receive the same training as a compounding pharmacist and must undergo annual assessment of competency in the compounding of hazardous sterile preparations.

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 the compounding of hazardous 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 the compounding of hazardous 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 hazardous 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^{21, 22}

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 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 equipment²³

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

Facilities for the compounding of hazardous sterile preparations 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 Useful references

5.3.1.1 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.

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

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

23 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>



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.

5.3.1.2 Prevention Guide – Safe Handling of Hazardous Drugs²⁴

In 2008, the Association paritaire pour la santé et la sécurité du travail du secteur affaires sociales (ASSTSAS; a joint sector-based association for occupational health and safety in the health and social services sector in the province of Quebec) published a guide pertaining to the risks associated with handling hazardous drugs and the preventive measures to be applied in a health care facility at the various stages of the preparation, distribution and administration of hazardous drugs.

The guide explains that the principles of precaution “apply unequivocally to all antineoplastic drugs, regardless of whether they are used in oncology or to treat other conditions (e.g., methotrexate for arthritis). However, some precautions could be adapted for other categories (e.g., hormones), based on the specific risks for each category”²⁵.

These Model Standards pertain mainly to hazardous compounded sterile preparations involving antineoplastic drugs, since these drugs account for the majority of hazardous sterile compounding undertaken in pharmacy.

5.3.1.3 NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings²⁶

The US Department of Health and Human Services, through its Centers for Disease Control and Prevention and the National Institute for Occupational Safety and Health (NIOSH), publishes and updates a list of hazardous drugs. This published list must be used by individual pharmacies to develop their own lists of hazardous drugs that require special handling precautions. A list of hazardous drugs used must be available at the pharmacy and must be reviewed at least every 12 months. Each of these drugs must be handled and disposed of properly.

In addition, in 2004 NIOSH published an alert on preventing occupational exposure to antineoplastic and other hazardous drugs²⁷.

24 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>

25 Association paritaire pour la santé et la sécurité du travail du secteur affaires sociales (ASSTSAS). Chapter 2: Risks related to the use of hazardous drugs. In: *Prevention guide – safe handling of hazardous drugs*. Montréal, QC: ASSTSAS; 2008. p. 2-2. Available from: <https://www.irsst.qc.ca/media/documents/PubIRSST/CG-002.pdf>

26 National Institute for Occupational Safety and Health (NIOSH). NIOSH list of antineoplastic and other hazardous drugs in healthcare settings 2012. Publ. No. 2012-150. Atlanta, GA: Department of Health and Human Services, Centers for Disease Control and Prevention, NIOSH; 2012 June. Available from: <http://www.cdc.gov/niosh/docs/2012-150/pdfs/2012-150.pdf>

27 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>



5.3.2 Facilities reserved for the compounding of hazardous sterile preparations

The requirements for facilities vary, depending on whether the sterile preparations to be compounded are hazardous or non-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 hazardous sterile preparations. Users should consult the companion document, “Model Standards for Pharmacy Compounding of Non-hazardous Sterile Preparations,” for requirements pertaining to the compounding of non-hazardous preparations.

5.3.2.1 Dimensions

Areas reserved for the compounding of 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 both to minimize the risk of airborne contamination in controlled rooms used for the compounding of hazardous sterile preparations and to minimize the exposure of personnel to hazardous products in the work environment. It must also be designed to achieve and maintain ISO Class 7 air quality for clean rooms and anterooms used for the compounding of hazardous sterile preparations²⁸ (see section 5.3.2.5, Table 2).

The air supplied to areas used for compounding 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 filter²⁹.

All sources that generate particles must be controlled to achieve and maintain the ISO class for clean rooms and anterooms used to compound hazardous sterile preparations³⁰.

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 hazardous sterile-product preparation (e.g., media fill).

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

29 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>

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



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 containment primary engineering controls (C-PECs) (e.g., biological safety cabinets [BSCs] or compounding aseptic containment isolators [CACIs]). The particle count may also be measured by a qualified certifier (*see* Appendices 5 and 6).

The return air from the clean room must be exhausted to the exterior of the building.

Return air exhausts should be installed at the bottom of walls³¹, 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 C-PEC) to ensure that the location of the return air exhausts 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 C-PEC (e.g., BSC or CACI) is located, and an anteroom, located next to the clean room.

See also section 5.3.2.6.

Clean room

The clean room is a room in which the 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 within the room and the spread of hazardous products outside the room.

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 contaminants into the room³² and the spread of hazardous drug contamination outside the room. 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 hazardous sterile preparations.

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

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



Contents

The C-PEC or C-PECs are installed in the clean room. For hazardous compounding, C-PECs may be BSCs or CACIs³³.

Many hazardous drugs can volatilize at room temperature. Therefore, they must be stored within a negative-pressure room. The storage area should have at least 12 air changes per hour (ACPH), with the air being completely exhausted to the exterior. Given these requirements, a facility may choose to construct a separate storage area for hazardous drugs. (*See also* subsection below, “Area for storing hazardous products”.)

Alternatively, hazardous sterile preparations and the refrigerator in which they are stored may be placed in the clean room for compounding hazardous sterile preparations. This approach ensures that the drugs are stored in a negative-pressure room with sufficient ACPH (since the clean room has at least 30 ACPH, with the air being completely exhausted to the exterior). The facility must ensure that air exhausts are placed so that they will remove particles generated within the storage area and the refrigerator and must also ensure sufficient ACPH to maintain an ISO Class 7 clean room. The use of equipment in the clean room is permitted as long as such use does not increase the generation of viable or non-viable particles within the clean room.

Anteroom³⁴

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: 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 anteroom and the non-controlled area must have windows to prevent accidents involving personnel entering or leaving through the doors. A window covering half the area of door may be sufficient.

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.

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.

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

- The first space or area, referred to as “dirty”, is located at the entrance to the anteroom, in the section adjacent to the non-controlled area. Although this area is referred to as “dirty,” it is considered to be free of chemical contamination when hazardous preparations are being compounded in the clean room.
- The second space or area, referred to as “clean”, is adjacent to the dirty area on one side and the clean room on the other. Although this area is referred to as “clean,” it is considered to be chemically contaminated when hazardous preparations are being compounded in the clean room.

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

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



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

Table 2 and Figure 1 illustrate the functional parameters of the clean room and the anteroom for the compounding of hazardous sterile preparations.

Use

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

The anteroom must contain the following items:

- PPE and storage space for 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;
- cytotoxic waste container;
- eyewash station³⁵, 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.

35 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/emer_showers.html



Supplies

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.

Table 2

Functional parameters of the clean room and anteroom for the compounding of hazardous sterile preparations
<p>General principles:</p> <ul style="list-style-type: none"> • Maintain negative pressure to prevent air that might be contaminated by hazardous products from leaving the clean room (principle of containment). • Ensure that construction quality is sufficient to guarantee that controlled rooms (i.e., rooms responsible for containment) are airtight. • Notwithstanding the two preceding principles, do not depressurize the clean room too much, so as to minimize penetration of non-filtered air through gaps in the construction (since no room will be perfectly airtight). • Maintain ISO Class 7 air quality (to prevent particles from entering the clean room). • Protect pharmacy personnel (by means of air exhausts). <p>To adhere to these principles, the following functional parameters must be met:</p> <ul style="list-style-type: none"> • The clean room must be kept under negative pressure relative to the anteroom³⁶. • The pressure of the clean room must be -2.5 Pa (equivalent to 0.01 inch water column) relative to surrounding areas (pharmacy or other)³⁷. • The pressure differential between the anteroom and the clean room ($P_B - P_C$; see Figure 1) must be at least 2.5 Pa to maintain unidirectional airflow from the anteroom to the clean room. • The pressure in the anteroom must be positive. The pressure differential must be at least 5.0 Pa relative to the pharmacy adjacent to the anteroom. • ISO Class 7 air quality must be maintained in the clean room and the anteroom under dynamic operating conditions³⁸. • There must be at least 30 air changes per hour (ACPH)³⁹ in the clean room and the anteroom. Depending on the size of the rooms and the number of people working in them, a greater number of ACPH may be required. • The return air from the clean room must be externally vented. • The temperature in the controlled rooms must be less than or equal to 20°C⁴⁰, 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 Pharmacists⁴¹. See also the pressure diagram for the anteroom and the clean room (Figure 1).</p>
ISO = International Organization for Standardization; PPE = personal protective equipment.

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

37 United States Pharmacopeial Convention (USP). General chapter <800>: hazardous drugs — handling in health care settings. Rockville, MD: USP; 2016.

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

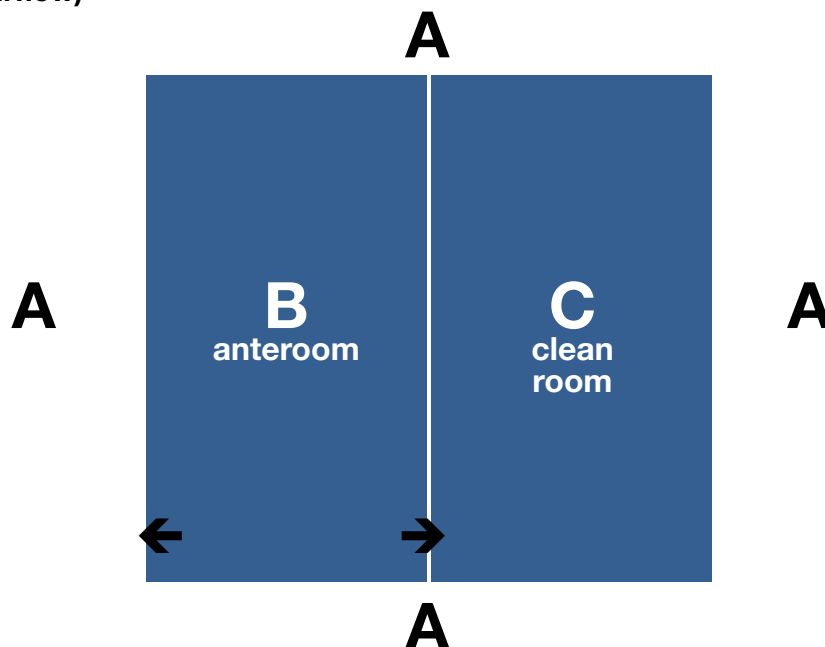
39 International Organization for Standardization (ISO). *ISO 14644-4 Cleanrooms and associated controlled environments – Part 4: Design, construction and start-up*. Geneva, Switzerland: ISO; 2001.

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

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



Figure 1: Pressure diagram for hazardous compounding (arrows indicate direction of airflow)



Pressure differentials:	
Pressure differentials to be maintained at all times:	1) $(P_B - P_A) \geq 5.0 \text{ Pa}$ 2) $(P_B - P_C) > 2.5 \text{ Pa}$ 3) $-2.5 \text{ Pa} < (P_C - P_A)$
Legend:	A = facilities environment B = anteroom C = clean room P = pressure Pa = pascal (SI unit of measure for pressure)

Given the PPE 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 must be restricted to personnel with specific responsibilities in the clean room.

To enable verification 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.

Area for unpacking hazardous products

If a hazardous product arrives from the manufacturer in an undamaged state, sealed in impermeable plastic, then no special precautions are necessary⁴².

42 United States Pharmacopeial Convention (USP). General chapter <800>: hazardous drugs — handling in health care settings . Rockville, MD: USP; 2016.



If a hazardous drug arrives in a damaged state and unpacking is required, a C-PEC will be needed. The C-PEC may be used just for unpacking the damaged product, or it may also be used for the compounding of non-sterile hazardous preparations⁴³.

Area for storing hazardous products

Hazardous products must be grouped and stored in a properly ventilated room with all air exhausted to the exterior⁴⁴. The storage area must have negative pressure relative to the adjacent rooms and must have at least 12 ACPH. It must be identified with the proper signage to indicate the presence of hazardous products⁴⁵.

Additional requirements for a hazardous products storage area are listed in Table 3.

Alternatively, hazardous sterile preparations and the refrigerator in which they are stored may be placed in the clean room for compounding hazardous sterile preparations. This approach ensures that the drugs are stored in a negative-pressure room with sufficient ACPH (since the clean room has at least 30 ACPH, with the air being completely exhausted to the exterior). The facility must ensure that air exhausts are placed so that they will remove particles generated within the storage area and the refrigerator and must also ensure sufficient ACPH to maintain an ISO Class 7 clean room.

Table 3

Requirements for a hazardous products storage area
<ul style="list-style-type: none"> • Area separate from unpacking area • Dedicated room • Negative pressure (-2.5 Pa) relative to surrounding areas • At least 12 air changes per hour (ACPH), with all air exhausted to the exterior • Presence of shelves with lips to prevent drug containers from falling off and breaking⁴⁶ • Storage spaces for hazardous products and preparations identified with the proper signage to indicate the presence of hazardous products⁴⁷ • Sufficient ventilation to prevent contamination from spreading to adjoining rooms⁴⁸

A facility may choose to construct a separate room for the storage of hazardous products. However, the storage of hazardous sterile products is permitted in the clean room (for more information, *see* section 5.3.2.5, above).

5.3.2.6 Shared facilities

Compounding of hazardous and non-hazardous sterile preparations

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

43 United States Pharmacopeial Convention (USP). General chapter <800>: hazardous drugs – handling in health care settings . Rockville, MD: USP; 2016.

44 Association paritaire pour la santé et la sécurité du travail du secteur affaires sociales (ASSTSAS). Chapter 6: Unpacking and storage. In: *Prevention guide – safe handling of hazardous drugs*. Montréal, QC: ASSTSAS; 2008. p. 6-4. Available from: <https://www.irsst.qc.ca/media/documents/PubIRSST/CG-002.pdf>

45 Association paritaire pour la santé et la sécurité du travail du secteur affaires sociales (ASSTSAS). Chapter 4: General preventive measures. In: *Prevention guide – safe handling of hazardous drugs*. Montréal, QC: ASSTSAS; 2008. p. 4-4. <https://www.irsst.qc.ca/media/documents/PubIRSST/CG-002.pdf>

46 Association paritaire pour la santé et la sécurité du travail du secteur affaires sociales (ASSTSAS). Chapter 6: Unpacking and storage. In: *Prevention guide – safe handling of hazardous drugs*. Montréal, QC: ASSTSAS; 2008. p. 6-4. Available from: <https://www.irsst.qc.ca/media/documents/PubIRSST/CG-002.pdf>

47 Association paritaire pour la santé et la sécurité du travail du secteur affaires sociales (ASSTSAS). Chapter 4: General preventive measures. In: *Prevention guide – safe handling of hazardous drugs*. Montréal, QC: ASSTSAS; 2008. p. 4-4. Available from: <https://www.irsst.qc.ca/media/documents/PubIRSST/CG-002.pdf>

48 Association paritaire pour la santé et la sécurité du travail du secteur affaires sociales (ASSTSAS). Chapter 7: Planning the oncology pharmacy. In: *Prevention guide – safe handling of hazardous drugs*. Montréal, QC: ASSTSAS; 2008. p. 7-9. Available from: <https://www.irsst.qc.ca/media/documents/PubIRSST/CG-002.pdf>



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 hazardous sterile preparations and the other for non-hazardous sterile preparations), they may share a single anteroom.

This layout is not recommended, but if space constraints dictate that facilities for compounding hazardous and non-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 of the companion document, “Model Standards for Pharmacy Compounding of Non-hazardous Sterile Preparations.”

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 section 5.3.2.5 of the current document.

Shared anteroom

The sole anteroom is connected to both clean rooms for the compounding of sterile preparations (hazardous and non-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 hazardous and non-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 hazardous sterile preparations and the clean room for the compounding of non-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 hygiene and donning of PPE. No drugs are stored in a shared anteroom.



Table 4**Functional parameters of a shared anteroom for the compounding of hazardous and non-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 Pa⁴⁹ (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 conditions⁵⁰.
- There must be at least 30 air changes per hour (ACPH)⁵¹. 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 temperature must not exceed 25°C.

Note: There is no requirement for relative humidity; refer to the recommendations of the Canadian Society of Hospital Pharmacists⁵².

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–NF⁵³ for compounding rooms used for the preparation of hazardous and non-hazardous sterile preparations.

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.

49 United States Pharmacopeial Convention (USP). Response provided by USP for a shared anteroom, March 21, 2012.

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

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

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

53 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 accumulate⁵⁴. 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 installed⁵⁵, 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 frame⁵⁶. 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 to ensure no increase in viable and non-viable particles. 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 to the side wall, at least 10–15 cm.
- There must be no carpets, rugs, “sticky mats” or anti-fatigue mats⁵⁷.

54 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>

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

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

57 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.

BSCs and CACIs must be connected to a notification system⁵⁸ to alert personnel to any unscheduled interruption or any alert related to the operation of the device outside compounding periods.

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.

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, disinfecting and decontamination.

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.

58 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



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 indicating cytotoxicity, the need for special care, hazards, restricted access, dress code).

5.3.2.12 Facility maintenance

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

The same PPE that is worn for the compounding of hazardous sterile preparations must be worn for any type of facility and equipment maintenance, including changing filters and pre-filters that have potentially been contaminated by hazardous products, even if the filters are accessible from outside controlled areas (anteroom and clean room).

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.

Filters used to exhaust air from clean rooms or C-PECs must be considered contaminated and must be handled with a level of care appropriate to protecting personnel and the environment. Where applicable, “bag in/bag out” containment systems may be used to enhance the safety of such operations.

5.3.3 Equipment

5.3.3.1 Containment Primary Engineering Control

Hazardous sterile preparations must be compounded inside a C-PEC. Examples of C-PECs for hazardous sterile preparations include Class II or Class III BSCs and CACIs⁵⁹. Oncology adjunctive therapies can also be prepared in these devices, if they are being compounded for the same patient as the hazardous sterile preparation. These adjunctive therapies must be handled and labeled to require hazardous drug precautions.

The C-PEC is located in the clean room. The device’s ventilation system and its HEPA filter serve to filter the air in the compounding environment. The C-PEC air quality must comply with ISO Class 5 specifications. The C-PEC must be externally ventilated.

59 United States Pharmacopeial Convention (USP). General chapter <800>: hazardous drugs — handling in health care settings . Rockville, MD: USP; 2016.



Before a C-PEC is used,

- personnel must read and understand the user's manual;
- the C-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 C-PEC must operate continuously, 24 hours a day⁶⁰. If the C-PEC has been turned off, it must be allowed to run for at least 30 minutes, or as recommended by the manufacturer, before decontamination, cleaning and disinfection and then compounding of hazardous sterile preparations are undertaken⁶¹.

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

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

If a CACI 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 containment primary engineering control and other furniture

The C-PEC and other pieces of furniture should be positioned to avoid interfering with facility ventilation systems^{62, 63, 64}.

To facilitate cleaning and disinfecting activities, such as cleaning the exterior of the C-PEC, and to avoid interfering with the operation of the C-PEC, there must be sufficient clearance around the C-PEC (usually 0.3 m⁶⁵). Some types of C-PEC can be built into the wall and sealed or wall-mounted and sealed, but this mode of installation is not possible with other types. When positioning a C-PEC, the manufacturer's recommendations must be strictly followed to avoid interfering with normal operation. During certification, a smoke test under dynamic conditions may be used to validate proper operation.

BSC⁶⁷

The BSC must be positioned in an ISO Class 7 clean room or better, under negative pressure and adjoining an ISO Class 7 anteroom. The BSC must not be placed near doors or other sources of drafts that might adversely affect unidirectional airflow.

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

60 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

61 United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013. p. 380.

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

63 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.

64 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>

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

66 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.

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



CACI⁶⁸

The CACI must be positioned in an ISO Class 7 clean room or better, under negative pressure and adjoining an ISO Class 7 anteroom.

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

- The room has negative pressure (at least 2.5 Pa negative pressure relative to adjacent spaces)⁶⁹.
- The room has at least 12 ACPH⁷⁰.
- The CACI 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 CACI.
- Particulate sampling from 15 to 30 cm upstream of the critical exposure site within the CACI used for hazardous sterile preparations shows ISO Class 5 air quality during compounding.
- 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 CACI.

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

- documentation indicating that the CACI 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).

Compounding personnel working in a CACI must comply with the garbing procedure for compounding of hazardous sterile preparations, both to maintain air quality and to protect themselves from spills.

Maintenance of containment primary engineering control

C-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 guides CAG-003, CAG-005 and CAG-002-2006 (current versions).

BSCs and CACIs must be certified⁷¹

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

C-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.

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

69 United States Pharmacopeial Convention (USP). General chapter <800>: hazardous drugs — handling in health care settings. Rockville, MD: USP; 2016.

70 United States Pharmacopeial Convention (USP). General chapter <800>: hazardous drugs — handling in health care settings. Rockville, MD: USP; 2016.

71 United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013. p. 374.



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 C-PECs and other equipment must be performed when no compounding is in progress, before cleaning and disinfection operations.

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

The sterile compounding supervisor must ensure that C-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 hazardous sterile preparations

Equipment used to compound hazardous 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.

The decision to place equipment, instruments or accessories not directly related to the compounding of hazardous sterile preparations (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.)⁷². The use of equipment and supplies in the anteroom and the clean room is permitted as long as such use 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. If they must be removed, they must be decontaminated.

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 C-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 disinfecting), then as needed, according to the manufacturer's recommendations. The balance must be calibrated before each use, after it is moved, after disinfecting 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.

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



Carts

If carts are used, one cart must be reserved for the “dirty” area of the anteroom and must remain there⁷³.

A second cart must be reserved for use in the “clean” area of the anteroom and in the clean room⁷⁴.

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.

Refrigerator and freezer

Choice

Refrigerators and freezers used to store medications must be commercial, biomedical-grade units^{75, 76, 77}. Domestic refrigerators and freezers must not be used.

Use and placement

Refrigerators and freezers designated for hazardous drugs must be used only for this purpose. They must not be used to store food or other medications/solutions, etc.

Hazardous sterile preparations and hazardous sterile drugs and the refrigerator and freezer in which they are stored may be placed in the clean room for compounding hazardous sterile preparations. An air exhaust must be placed behind the refrigerator or freezer to remove any particles generated by the unit. There must be sufficient ACPH in the clean room to maintain the ISO Class 7 air quality classification.

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.

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

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

75 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>

76 Public Health Agency of Canada (PHAC). *National vaccine storage and handling guidelines for immunization providers*. Ottawa, ON: PHAC; 2007. p. 22.

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



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).

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 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, disinfecting and decontamination products. Personal electronic devices or accessories (cell phone, iPods, earbuds) are not permitted in the anteroom or clean room.

Hazardous waste containers

A sufficient number of hazardous waste containers of suitable size and made of materials resistant to damage from cleaning, disinfecting and decontamination products must be available. Waste containers must be closable, to limit the spread of vapours. The exterior of each waste container must be decontaminated before it is removed from the controlled area.

The waste shall be removed once a day, at a time when no compounding is occurring. Waste containers must be identified with appropriate hazardous materials symbols (e.g., pictogram indicating cytotoxicity).



5.3.3.3 Personal protective equipment and clothing⁷⁸

PPE adapted and approved for the compounding of hazardous sterile preparations must be worn during such compounding activities.

Gloves

Gloves used in the clean room, in the clean area of the anteroom and during aseptic processes in all C-PECs (including isolators) must be

- non-powdered;
- compliant with standard D-6978-05 of ASTM International (formerly the American Society for Testing and Materials);
- sterile (outer glove only).

Non-sterile gloves that meet the ASTM International standard can be used in unpacking areas, the “dirty” area of the anteroom and storage areas and can be worn under sterile gloves for aseptic processes.

For the following activities, personnel must wear *two pairs of gloves* meeting the ASTM International standard:

- unpacking;
- cleaning and disinfecting the clean room;
- disinfecting the C-PEC;
- compounding of hazardous preparations;
- managing a spill;
- disposing of hazardous products.

Glove changes

Both pairs of gloves must be discarded and replaced at the earliest of the manufacturer’s limit for permeation of the gloves, every 30 minutes^{79, 80, 81} or immediately if a tear, puncture or contamination has occurred or is suspected.

Gown

The gown must have been tested by the manufacturer for resistance to permeability by hazardous drugs^{82, 83}. It must close in the back (i.e., no open front), and it must have long sleeves with fitted cuffs at the wrists.

78 Association paritaire pour la santé et la sécurité du travail du secteur affaires sociales (ASSTSAS). Chapter 4: General preventive measures. In: *Prevention guide – safe handling of hazardous drugs*. Montréal, QC: ASSTSAS; 2008. pp. 4-5 to 4-11. Available from: <https://www.irsst.qc.ca/media/documents/PubIRSST/CG-002.pdf>

79 Buchanan EC, Schneider PJ. *Compounding sterile preparations*. 3rd ed. Bethesda, MD: American Society of Health-System Pharmacists; 2009. p. 85.

80 Wallemacq PE, Capron A, Vanbinst R, Boeckmans E, Gillard J, Favier B, Permeability of 13 gloves to 13 cytotoxic agents under controlled dynamic conditions. *Am J Health Syst Pharm*. 2006;63(6):547-56.

81 Association paritaire pour la santé et la sécurité du travail du secteur affaires sociales (ASSTSAS). Chapter 4: General preventive measures. In: *Prevention guide – safe handling of hazardous drugs*. Montréal, QC: ASSTSAS; 2008. p. 4-5. Available from: <https://www.irsst.qc.ca/media/documents/PubIRSST/CG-002.pdf>

82 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. p. 13. Available from: <http://www.cdc.gov/niosh/docs/2004-165/pdfs/2004-165.pdf>

83 Buchanan EC, Schneider PJ. *Compounding sterile preparations*. 3rd ed. Bethesda, MD: American Society of Health-System Pharmacists; 2009. p. 87.



The gown must be discarded and replaced at the earliest of the manufacturer's time limit for permeation of the gown or after 2–3 hours of continuous compounding work^{84, 85} or after each removal or after a contamination has occurred or is suspected.

A gown is required for unpacking a damaged hazardous drug or if a spill of hazardous material has occurred⁸⁶.

Hair cover

A disposable hair cover must be worn during the compounding of hazardous sterile preparations. It must be changed after each removal or if it becomes contaminated⁸⁷.

Mask

Table 5 outlines the uses for and limitations of different types of masks.

No mask is needed for unpacking hazardous drugs that have been received from the supplier in impervious plastic. However, if a hazardous drug shipment has been damaged before receipt, a chemical cartridge respirator is required during unpacking⁸⁸.

Surgical masks do not provide respiratory protection against drug exposure and therefore should not be used when respiratory protection from hazardous drug exposure is required.

For most activities, an N95 or N100 mask (NIOSH-approved) will protect against airborne particles. However, N95 or N100 masks offer no protection from vapours, gases and little protection from direct liquid splashes.

A chemical cartridge respirator with a pre-filter must be worn in the presence of vapours, gas and particles (e.g., dust) or if there has been a spill. A cartridge that protects against the chlorine found in chlorinated disinfectants used for cleaning the C-PEC or for chemical decontamination after a spill may also be considered, to help prevent irritation of airways.

Any mask (including N95 or N100 masks and chemical cartridge respirators) must first be fit-tested.

The mask must be changed at the earliest of the following: after 3.5 hours of continuous compounding work, after each removal or if contamination has occurred or is suspected.

84 Association paritaire pour la santé et la sécurité du travail du secteur affaires sociales (ASSTSAS). Chapter 4: General preventive measures. In: *Prevention guide – safe handling of hazardous drugs*. Montréal, QC: ASSTSAS; 2008. p. 4-6. Available from: <https://www.irsst.qc.ca/media/documents/PubIRSST/CG-002.pdf>

85 United States Pharmacopeial Convention (USP). General chapter <800>: hazardous drugs – handling in health care settings . Rockville, MD: USP; 2016.

86 United States Pharmacopeial Convention (USP). General chapter <800>: hazardous drugs – handling in health care settings . Rockville, MD: USP; 2016.

87 Association paritaire pour la santé et la sécurité du travail du secteur affaires sociales (ASSTSAS). Chapter 4: General preventive measures. In: *Prevention guide – safe handling of hazardous drugs*. Montréal, QC: ASSTSAS; 2008. p. 4-6. Available from: <https://www.irsst.qc.ca/media/documents/PubIRSST/CG-002.pdf>

88 United States Pharmacopeial Convention (USP). General chapter <800>: hazardous drugs – handling in health care settings . Rockville, MD: USP; 2016.



Table 5

Masks and chemical cartridge respirators				
Type of mask	Activity	Operating conditions	Filters	Notes
N95 or N100 (NIOSH-approved)	Compounding of hazardous sterile preparations	ISO Class 7 compounding room under negative pressure BSC with front window closed Compounding in a CACI	N/A	Must be a mask specific for health care workers (not for construction workers) Dust protection required
Chemical cartridge respirator with full face-piece or chemical cartridge respirator with face shield and goggles	Manipulation with splash risk Cleaning up a spill Deactivating, decontaminating and cleaning underneath the work surface of a C-PEC Unpacking suspected damaged drugs from the supplier	ISO Class 7 compounding room under negative pressure BSC/CACI with front window open C-PEC for unpacking suspected damaged drugs Anywhere a spill has occurred	For organic vapour, gas and dust	Refer to manufacturer's instructions to determine frequency of filter change
BSC = biological safety cabinet; CACI = compounding aseptic containment isolator; C-PEC = containment primary engineering control; ISO = International Organization for Standardization; N/A = not applicable; NIOSH = National Institute for Occupational Safety and Health (United States).				

Goggles and face shield or full face-piece respirator

Goggles and a face shield or full face-piece respirator must be worn when working at or above eye level, when deactivating, decontaminating and cleaning underneath the work surface of a C-PEC, when cleaning up a spill, when there is risk of splashes to the face and eyes and when unpacking suspected damaged drugs.

Shoe covers

Shoe covers prevent the contamination of shoes and subsequent spread of contamination to other areas of the facility⁸⁹. Two pairs of disposable shoe covers are required at all times in the clean area of the anteroom and in the clean room, even if dedicated shoes are worn. The shoe covers must be changed after each removal or in the event of contamination, spill or breakage⁹⁰. Shoe covers worn in hazardous drug compounding areas are not to be worn outside the controlled area.

Beard cover

If the compounder has facial hair, a disposable beard cover must be worn while compounding hazardous sterile preparations.

89 Association paritaire pour la santé et la sécurité du travail du secteur affaires sociales (ASSTSAS). Chapter 4: General preventive measures. In: *Prevention guide – safe handling of hazardous drugs*. Montréal, QC: ASSTSAS; 2008. p. 4-8. Available from: <https://www.irsst.qc.ca/media/documents/PublRSST/CG-002.pdf>

90 Association paritaire pour la santé et la sécurité du travail du secteur affaires sociales (ASSTSAS). Chapter 4: General preventive measures. In: *Prevention guide – safe handling of hazardous drugs*. Montréal, QC: ASSTSAS; 2008. p. 4-6. Available from: <https://www.irsst.qc.ca/media/documents/PublRSST/CG-002.pdf>



The beard cover must be changed at the earliest of the following: after 3.5 hours of continuous work, after each removal or if contamination occurs or is suspected.

Uniform

Compounding personnel shall wear clean room scrubs, not street clothes. Use of clean room scrubs reduces the risk of contaminating the environment through clothing.

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

5.3.4.1 General

Cleaning and disinfecting (housekeeping) in controlled areas must be performed to ensure the cleanliness required for the quality and integrity of final compounded sterile preparations⁹¹.

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 controlled areas⁹².

5.3.4.2 Surface decontamination, deactivation and disinfection

When hazardous sterile preparations are compounded, cleaning of the premises and equipment must also eliminate chemical contamination from the hazardous products used. Methods used include decontamination, deactivation and disinfection.

Decontamination

Decontamination involves the transfer of a hazardous drug contaminant from a fixed surface (e.g., counter, bag of solution) to a disposable surface (e.g., wipe, cloth). The wipe is then contained and discarded as hazardous waste.

Many solutions can be used for decontamination, for example, 70% isopropyl alcohol, sterile water, hydrogen peroxide and sodium hypochlorite. (See sections 5.3.4.6 and 6.6.4.3 for frequency of surface decontamination.)

Deactivation

Deactivation is the treatment of a hazardous drug to create a less hazardous agent, for example, by chemical deactivation. The material safety data sheets for some hazardous drugs recommend sodium hypochlorite for this purpose, usually as a 2% solution. This compound will corrode stainless steel surfaces, so it must then be neutralized with sodium thiosulphate or removed with a germicidal detergent. Surface Safe™ (Hospira) is a commercially available system of wipes containing both of these substances⁹³. Sodium hypochlorite also has an additional germicidal effect for disinfection⁹⁴.

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

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

93 Association paritaire pour la santé et la sécurité du travail du secteur affaires sociales (ASSTSAS). Chapter 13: Hygiene and sanitation. In: *Prevention guide — safe handling of hazardous drugs*. Montréal, QC: ASSTSAS; 2008. p. 13-2. Available from: <https://www.irsst.qc.ca/media/documents/PubIRSST/CG-002.pdf>

94 Kastango ES, Douglass K. Quality assurance for sterile products. *Int J Pharm Compound*. 2001;5(4):246.



Disinfection

Disinfection is the process of destroying microorganisms. (See sections 5.3.4.6 and 6.6.4.3 for frequency of disinfection).

5.3.4.3 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 disinfected.

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 agent⁹⁵.

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

5.3.4.4 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 the compounding of hazardous sterile preparations^{96, 97}.

Non-shedding⁹⁸ equipment must be used for cleaning controlled areas. This equipment (mop, towels, etc.) should be disposable.

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.

5.3.4.5 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 two pairs of ASTM International–approved gloves before starting work. The outer gloves must be sterile.

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

96 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.

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

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



5.3.4.6 Cleaning frequency

Cleaning and disinfecting procedures must include surface decontamination followed by disinfection at regular intervals and at specific locations as described below.

The minimum frequency of cleaning and disinfecting in clean rooms and anterooms will be either daily or monthly⁹⁹.

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

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

In addition, waste and garbage must be removed daily.

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

- walls
- ceiling
- shelves
- area outside the C-PEC (this area must be decontaminated along with cleaning and disinfecting)

Cleaning should be done from the “cleanest” area to the “dirtiest” area. Cleaning should also take into account the minimization of chemical contamination moving from less chemically contaminated areas to more chemically contaminated.

Forms or schedules used to document cleaning, decontamination 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 C-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 practices of the respective provincial/territorial regulatory authority and in accordance with the principles of confidentiality.

99 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.



6. PRODUCT AND PREPARATION REQUIREMENTS

6.1 Beyond-use date and dating methods

6.1.1 Beyond-use date of preparations

For the purposes of these Model Standards, administration of the hazardous compounded sterile preparation must begin before the BUD has passed¹⁰⁰.

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^{101, 102, 103} according to reference texts
- storage time related to risk of microbial contamination¹⁰⁴

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 sterility tests. Preparations may be released once the results of sterility testing 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 used for the compounding of hazardous sterile preparations, as specified in the following three sections (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 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.

100 United States Pharmacopeial Convention (USP). General chapter <795>: pharmaceutical compounding — nonsterile preparations. USP 36. Rockville, MD: USP; 2011.

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

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

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

104 United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013. pp. 365-7.

- If the vial is punctured in a C-PEC that maintains ISO Class 5 air quality, the BUD is 6 hours¹⁰⁵.
- Six hours after initial needle puncture, the vial can no longer be used. Once the vial is removed from the ISO Class 5 C-PEC, it must be discarded.
- To properly manage risk, a label must be affixed to the vial indicating the time of initial needle puncture.
- The contents of a vial cannot 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 phase 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 contamination¹⁰⁶.

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 (Table 6) apply to preparations compounded in a compliant, certified C-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 CACI 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 determining the risk level and 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."

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

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



Table 6

Contamination risk levels ^{107, 108}		
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 hazardous compounded sterile preparations, according to risk of microbial contamination ¹⁰⁹			
	BUD without sterility testing		
Risk of contamination	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 test¹¹⁰

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

- when hazardous 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

Hazardous sterile preparations do not qualify as immediate-use preparations (as defined in USP General Chapter <797>).

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

108 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.

109 United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013. pp. 365-7.

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



6.1.5 Beyond-use times of 12 hours or less for preparations compounded in segregated areas¹¹¹

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

- The segregated area has walls to separate the room from other areas.
- The C-PEC is certified every 6 months and maintains ISO Class 5 air quality or better.
- The room has a minimum of 12 ACPH.
- The room maintains negative pressure of at least -2.5 Pa relative to adjacent spaces.
- Only low- or medium-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 1 metre away from the C-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 disinfecting¹¹².

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; 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.

6.2 Compounded sterile preparation protocols

Protocols for the compounding of hazardous 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

111 United States Pharmacopeial Convention (USP). General chapter <800>: hazardous drugs — handling in health care settings . Rockville, MD: USP; 2016.

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



- BUD
- references
- draft and revision date
- pharmacist's signature

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

All protocols for hazardous 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 hazardous 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 hazardous sterile preparations made in batches.

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

6.3.1 Hazardous compounded sterile preparation log for one patient (individual preparations)

The hazardous 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 Hazardous compounded sterile preparation log for batch preparations

The log for hazardous compounded 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 hazardous 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 hazardous 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 hazardous sterile preparations

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

Regardless of which type of C-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 quality¹¹³. 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, compounding personnel must¹¹⁴:

- remove personal outer garments (e.g., coat, hat, jacket, scarf, sweater, vest, boots and outdoor shoes);

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

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



- 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);
- 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 polish¹¹⁵ 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 prohibited¹¹⁶.
- 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 area 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 BSC should also be avoided.

6.6 Aseptic compounding of hazardous sterile preparations^{117, 118}

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;

115 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 Recomm Rep.* 2002;51(RR-16):1-48. Available from: <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5116a1.htm>

116 United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013. p. 380.

117 Association paritaire pour la santé et la sécurité du travail du secteur affaires sociales (ASSTSAS). Chater 8: Drug preparation. In: *Prevention guide — safe handling of hazardous drugs*. Montréal, QC: ASSTSAS; 2008. Available from: <https://www.irsst.qc.ca/media/documents/PublRSST/CG-002.pdf>

118 American Society of Health-System Pharmacists. ASHP guidelines on handling hazardous drugs. *Am J Health Syst Pharm.* 2006;63(12):1172-93.



- disinfecting the C-PEC;
- disinfecting and introducing products and equipment into the C-PEC;
- using aseptic techniques to compound hazardous sterile preparations in the C-PEC;
- decontaminating final hazardous compounded sterile preparations;
- verifying, labelling and packaging final hazardous compounded sterile preparations.

Personnel must develop work techniques to minimize the risk of cross-contamination and microbial contamination, to avoid errors and to maximize performance of the C-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 activities¹¹⁹.

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 hazardous sterile preparation and must validate the preparations log.

Exposure of critical sites must be limited to a C-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 C-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, face masks and 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 alcohol-based hand rub (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.

¹¹⁹ United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013. p. 380.



- 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.
- For compounding hazardous preparations, don two pairs of gloves. The first (inner) pair of gloves goes under the sleeves of the gown, while the second (outer) pair must be pulled up over the gown cuffs. The outer gloves must be sterile.

This hand-washing sequence must be documented in the policies and procedures and updated as appropriate¹²⁰.

6.6.2.2 Garbing

PPE must be worn during the compounding of hazardous sterile preparations, regardless of the type of C-PEC that is used¹²¹.

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

The following general garbing sequence 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 two pairs of 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 also 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 gloves and routinely disinfect them with sterile 70% isopropyl alcohol or equivalent agent during the compounding process.

All compounding personnel must wear two pairs of gloves. The first (inner) pair of gloves goes under the sleeves of the gown, while the second (outer) pair must be pulled up over the gown cuffs. The outer gloves must be sterile.

Two pairs of shoe covers are required at all times in the clean area of the anteroom and the clean room.

When the compounding of hazardous sterile preparations is complete, personnel must remove the PPE following an established technique and sequence, to minimize the risk of chemical contamination, as set out in a detailed procedure developed by the facility. Personnel must dispose of soiled PPE in a container for cytotoxic waste and must then wash their hands before exiting the compounding area and performing any other activity.

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

121 Buchanan EC, Schneider PJ. *Compounding sterile preparations*. 3rd ed. Bethesda, MD: American Society of Health-System Pharmacists; 2009. Personnel cleansing and garbing.



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 after 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 room or the antechamber of a CACI¹²². Disinfection of equipment and products is performed by wiping (not spraying) with sterile 70% isopropyl alcohol. Non-shedding wipes or swabs must be used for disinfection. The wipes or swabs must be changed regularly during disinfection of products and equipment.

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 Surface decontamination, deactivation and disinfection of the containment primary engineering control

Only compounding personnel who have successfully achieved the competencies required for sterile compounding are allowed to decontaminate, deactivate and disinfect the C-PEC, according to the following steps:

- Perform hand and forearm hygiene and garbing procedures.
- Perform decontamination, deactivation and disinfection methods as described in the pharmacy’s procedures (respecting the specifications in terms of equipment, sequence, movements, frequency, etc.).

During decontamination, deactivation and disinfection, only the person performing these activities should be present in the clean room¹²³.

Decontamination, deactivation and disinfection tasks performed must be recorded in the general maintenance log.

6.6.4.1 Requirements for cleaning and disinfecting

Personnel must comply with the following requirements for cleaning and disinfecting:

- Disinfect non-powdered sterile gloves with sterile 70% isopropyl alcohol and allow to dry before starting to clean and disinfect the C-PEC.
- Ensure that the head and upper body do not enter the C-PEC.
- Use non-shedding, disposable wipes.
- Avoid contaminating the surface of wipes used for cleaning and disinfecting.

122 United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013. pp. 376, 379.

123 BC Cancer Agency (BCCA). Module 1: Safe handling of hazardous drugs. In: *BC Cancer Agency pharmacy practice standards for hazardous drugs*. Vancouver, BC: BCCA; 2012. Available from: <http://www.bccancer.bc.ca/health-professionals/professional-resources/pharmacy/safe-handling-manual>



- Change wipes after disinfection of each section of the C-PEC.
- Disinfect the BSC or CACI with sterile 70% isopropyl alcohol or another disinfecting agent, using sterile wipes, 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 C-PEC¹²⁴.
- Record cleaning and disinfecting activities in the general 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.

6.6.4.2 Decontamination of the containment primary engineering control

On its own, sterile 70% isopropyl alcohol cannot be used to decontaminate hazardous drugs and may in fact spread any chemical contamination that is present to other surfaces^{125, 126, 127}. Therefore, for daily activities such as disinfecting the inside of a C-PEC, a surface decontamination step using an appropriate agent¹²⁸ must precede the usual disinfection step with sterile 70% isopropyl alcohol.

6.6.4.3 Frequency of surface decontamination, deactivation and disinfection of the containment primary engineering control

Preparation of the interior surfaces of the C-PEC through surface decontamination followed by disinfection is a critical step in the aseptic preparation process. This step is to be performed by compounding personnel according to the frequencies set out in Table 8. If decontamination, deactivation and disinfection are performed at a different frequency, it should be established and justified on the basis of environmental control results.

The material safety data sheets for some hazardous products indicate that they can be deactivated by sodium hypochlorite. This compound will corrode stainless steel surfaces, so application of sodium hypochlorite is followed by sodium thiosulphate (for neutralization) or a germicidal detergent (for removal).

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

125 Sessink PJM, Boer KA, Scheefhals APH, Anzion RB, Box RP. Occupational exposure to antineoplastic agents at several departments in a hospital. Environmental contamination and excretion of cyclophosphamide and ifosfamide in urine of exposed workers. *Int Arch Occup Environ Health*. 1992;64(2):105-12.

126 Dorr RT, Alberts DS. Topical absorption and inactivation of cytotoxic anticancer agents in vitro. *Cancer*. 1992;70(4 Suppl):983-7.

127 American Society of Health-System Pharmacists. ASHP guidelines on handling hazardous drugs. *Am J Health Syst Pharm*. 2006;63(12):1172-93.

128 Association paritaire pour la santé et la sécurité du travail du secteur affaires sociales (ASSTSAS). Chapter 7: Planning the oncology pharmacy. In: *Prevention guide — safe handling of hazardous drugs*. Montréal, QC: ASSTSAS; 2008. p. 7-3. Available from: <https://www.irsst.qc.ca/media/documents/PubIRSST/CG-002.pdf>



Table 8

Minimum frequency of surface decontamination, deactivation and disinfection of the inside of a biological safety cabinet (BSC) or compounding aseptic containment isolator (CACI)				
Surface	Frequency ^{129,130,131,132,133}	Decontamination*	Deactivation†	Disinfection‡
Work surface in BSC or CACI	- Before start of compounding			✓
Work surface in BSC or CACI	- On each preparation change, upon removal from BSC or CACI - At the start or end of each shift - When surface contamination is suspected - If there has been non-compliance with aseptic techniques	✓		✓
All surfaces inside BSC or CACI	- At start of workday - At start of workday if BSC or CACI has not been used for one or more days - When there has been a spill - Before and after certification - After service interruption (ex power outage) - If the C-PEC is moved	✓		✓
All surfaces inside BSC or CACI and subfloor of BSC or CACI	- Weekly, at the end of a workday or as recommended by manufacturer	✓	✓	✓
*Surface decontamination = application of a decontaminating agent †Deactivation = application of sodium hypochlorite followed by sodium thiosulphate or a decontaminating agent ‡Disinfection = application of sterile 70% isopropyl alcohol.				

6.6.5 Aseptic technique for compounding hazardous sterile preparations

6.6.5.1 General

Compounding personnel must use first air and meticulous aseptic technique when preparing hazardous compounded sterile preparations. 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 C-PEC must be decontaminated and disinfected before another preparation is started.

129 BC Cancer Agency (BCCA). Module 1: Safe handling of hazardous drugs. In: *BC Cancer Agency pharmacy practice standards for hazardous drugs*. Vancouver, BC: BCCA; 2012. p. 11. Available from: <http://www.bccancer.bc.ca/health-professionals/professional-resources/pharmacy/safe-handling-manual>

130 American Society of Health-System Pharmacists. ASHP guidelines on handling hazardous drugs. *Am J Health Syst Pharm*. 2006;63(12):1172-93.

131 McElhiney LF. Preparing nonsterile and sterile hazardous compounds in an institutional setting. *Int J Pharm Compound*. 2009;13(4):300-10.

132 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. p. 5. Available from: https://www.osha.gov/dts/osta/otm/otm_vi/otm_vi_2.html

133 Association paritaire pour la santé et la sécurité du travail du secteur affaires sociales (ASSTSAS). Chapter 13: Hygiene and sanitation. In: *Prevention guide — safe handling of hazardous drugs*. Montréal, QC: ASSTSAS; 2008. pp. 13-2 and 13-3. Available from: <https://www.irsst.qc.ca/media/documents/PubIRSST/CG-002.pdf>

Gloved hands must be disinfected with sterile 70% isopropyl alcohol before re-introduction into the C-PEC or after gloves have come into contact with a microbiologically contaminated surface¹³⁴. For the frequency and circumstances of glove changes, *see* section 5.3.3.3.

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 C-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 C-PEC, vials must not be allowed to accumulate in the C-PEC.

6.6.5.2 Aspects of compounding hazardous preparations

Compounding personnel must adhere to the following requirements when working inside the C-PEC:

- When diluting powder or withdrawing liquids, use a ventilated system equipped with a 0.22- μm hydrophobic filter.
- When withdrawing a hazardous solution, comply with the maximum fill limit of the syringe, i.e., 75% (3/4) of total syringe capacity.
- When dispensing a hazardous preparation in a syringe, use a protective Luer-Lok safety tip system.
- If possible, use a closed-transfer system (since the steps described above do not completely eliminate the risk of exposure to the hazardous preparation).
- Discard all materials used during compounding into a marked waste container specifically designated for hazardous products.
- Before removing a container holding a final hazardous compounded sterile preparation from the C-PEC, follow the surface decontamination procedure¹³⁵ on all surfaces of the container.
- While the final container is still inside the C-PEC¹³⁶, compounding personnel must label it and place it in a sealable plastic bag¹³⁷. All final hazardous compounded sterile preparations must be marked “cytotoxic.”

6.6.6 Verification of final hazardous compounded sterile preparations

6.6.6.1 Role of personnel in verification

The sterile compounding supervisor must perform the following activities:

- ensure that all hazardous compounded sterile preparations comply with compounding protocols;

134 United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013. p. 380.

135 Association paritaire pour la santé et la sécurité du travail du secteur affaires sociales (ASSTSAS). Chapter 8: Drug preparation. In: *Prevention guide — safe handling of hazardous drugs*. Montréal, QC: ASSTSAS; 2008. p. 8-7. Available from: <https://www.irsst.qc.ca/media/documents/PubIRSST/CG-002.pdf>

136 Association paritaire pour la santé et la sécurité du travail du secteur affaires sociales (ASSTSAS). Chapter 8: Drug preparation. In: *Prevention guide — safe handling of hazardous drugs*. Montréal, QC: ASSTSAS; 2008. p. 8-7. Available from: <https://www.irsst.qc.ca/media/documents/PubIRSST/CG-002.pdf>

137 Association paritaire pour la santé et la sécurité du travail du secteur affaires sociales (ASSTSAS). Chapter 8: Drug preparation. In: *Prevention guide — safe handling of hazardous drugs*. Montréal, QC: ASSTSAS; 2008. p. 8-7. Available from: <https://www.irsst.qc.ca/media/documents/PubIRSST/CG-002.pdf>



- 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 hazardous 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 hazardous compounded sterile preparations must be cooled in the refrigerator before being placed in a cooler).

If the person performing verification duties enters the clean room, he or she must be garbed exactly the same as compounding personnel (*see* section 6.6.2.2). If verification occurs in the anteroom (i.e., via camera or image capture), the person performing verification must wear a hair cover, gown, two pairs of gloves meeting ASTM International standards and shoe covers.

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 C-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 C-PEC) with a camera connected to a monitor. Such verification must be performed before the hazardous 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 hazardous 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 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 integrity¹³⁸.

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

¹³⁸ United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013. p. 381.



6.6.7 Labelling of final hazardous compounded sterile preparations

6.6.7.1 General

The sterile compounding supervisor must establish a policy for the labelling of hazardous 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 hazardous 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 hazardous 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 hazardous compounded sterile preparations;
- each unit of a hazardous compounded sterile preparation for an individual patient, along with required auxiliary labels;
- each unit of hazardous 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 hazardous 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.

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 hazardous 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 cytotoxic);
- storage method;
- date when the hazardous 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.

The package must be appropriate to maintain the stability and integrity of the preparation.

6.7.1 Packaging process

During packaging, compounding personnel must

- put each final hazardous compounded sterile preparation in a clear plastic bag (or an amber bag, if the preparation must be protected from light);
- 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., pictogram indicating cytotoxicity);
- indicate transport precautions (e.g., temperature, fragility, safety) and instructions (name and address of the patient) on the outside packaging of each item.



6.7.2 Packaging procedure

To maintain the integrity of hazardous compounded sterile preparations and the safety of patients and delivery personnel, the sterile compounding supervisor must develop and implement a packaging procedure for final hazardous 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 hazardous compounded sterile preparation during transport and to protect the carrier;
- equipment to be used to ensure that packaging protects hazardous compounded sterile preparations against freezing and excessive heat (for hazardous compounded sterile preparations requiring refrigeration, the packaging must maintain a temperature between 2°C and 8°C and for hazardous 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 hazardous 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 hazardous compounded sterile preparations, unless information is available demonstrating the product's stability at these temperatures.

6.8 Receipt and storage of hazardous products¹³⁹

A sample procedure for receiving, unpacking and storing hazardous products is presented in Appendix 9.

6.8.1 Receipt of hazardous products

Products used for preparations must be unpacked outside of controlled areas (clean room and anteroom), to limit the introduction of dust and particles into the controlled areas.

If a shipping container for hazardous drugs appears damaged upon receipt, there are two options:

- Seal the package without opening it. Contact the supplier. If the package is to be returned to the supplier, place inside an impervious container and label the impervious container as hazardous. If the supplier declines the return, then dispose of as hazardous waste.
- Seal the container in an impervious container. Unpack the shipping container in a C-PEC used for compounding of non-sterile hazardous preparations. Place a plastic-backed preparation mat on the work surface of the C-PEC. Open the package and remove any usable items. Wipe the outside of these items with a disposable wipe. Place the damaged item(s) in an impervious container. Label the impervious container as hazardous. Contact the supplier for instructions on returning the damaged items. (*See also* section 6.11.2.) If the supplier declines the return, dispose of as hazardous waste. Deactivate, decontaminate and clean the C-PEC. Discard the mat and cleaning disposables as hazardous waste.

6.8.1.1 Containers and packaging for goods received

A container, box or outside bag containing an order of hazardous materials may be considered not chemically contaminated and may be returned to the supplier if so arranged.

Packaging within delivery containers (e.g., cartons, bubble wrap, foam, filling materials) that has not

¹³⁹ United States Pharmacopeial Convention (USP). General chapter <1079>: good storage and shipping practices. In: *USP pharmacists' pharmacopeia*. Rockville, MD: USP; 2008–2009. p. 880.



come into direct contact with product vials may also be considered not chemically contaminated and may be discarded in regular waste containers. These materials should not be used for other purposes.

If a spill has occurred inside the container, box or outside bag, then all packaging materials must be considered chemically contaminated and must be discarded in a hazardous (cytotoxic) waste container.

Manufacturer's boxes or individual packaging that has been in direct contact with vials containing hazardous products is to be considered chemically contaminated and must be discarded in a hazardous (cytotoxic) waste container.

6.8.1.2 Garbing of personnel for unpacking

For unpacking intact hazardous products that have been received from the supplier sealed in impervious plastic, the following garb is required¹⁴⁰.

- two pairs of ASTM International–approved gloves

For unpacking potentially damaged hazardous products, the following garb is required¹⁴¹:

- two pairs of ASTM International–approved gloves
- gown approved for the compounding of hazardous sterile preparations
- hair, face, beard and shoe covers
- eye protection (goggles) and a face shield or full face-piece respirator
- chemical cartridge respirator

Damaged hazardous drugs must be unpacked in a C-PEC used for compounding of non-sterile hazardous preparations.

6.8.2 Storage of hazardous products

6.8.2.1 Storage criteria

The sterile compounding supervisor must develop a storage procedure (*see* Appendix 4), and this procedure must be followed at all times. In particular, hazardous products must be stored separately from non-hazardous products. In addition, product storage conditions specified by the manufacturer must be strictly observed, regardless of where the products are stored (warehouse, pharmacy, delivery vehicle, delivery loading dock, etc.).

Hazardous products must be stored in a well-ventilated room (about 12 ACPH)¹⁴² or in a dedicated biomedical refrigerator or freezer (*see* section 5.3.2.5, subsection “Area for storing hazardous products”).

6.8.2.2 Temperature control

For final hazardous compounded sterile preparations or hazardous products used for such preparations, the storage temperature must be controlled and must remain within the limits specified in Appendix 10, and within the range specified by the BUDs of final preparations and products, regardless of the season. Information on monitoring of temperature in the storage area for hazardous products and the refrigerator or freezer must be recorded in the general maintenance log¹⁴³.

140 United States Pharmacopeial Convention (USP). General chapter <800>: hazardous drugs — handling in health care settings. Rockville, MD: USP; 2016.

141 United States Pharmacopeial Convention (USP). General chapter <800>: hazardous drugs — handling in health care settings. Rockville, MD: USP; 2016.

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

143 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 if the storage temperature exceeds acceptable variations and when refrigerators and freezers are being cleaned.

6.8.2.3 Verification of stored products

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

Preparations that have exceeded their BUDs must be discarded promptly.

6.9 Transport and delivery of hazardous compounded sterile preparations

Policies and procedures must be developed and implemented for the transport of hazardous compounded sterile preparations and their delivery to patient care units, pharmacists and patients (*see* Appendix 4). A policy for return of expired or unused hazardous 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 hazardous 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, including the procedure for dealing with accidental exposure or spills.

The pharmacist or pharmacy technician must dispose of any unused hazardous compounded sterile preparations 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 tampering¹⁴⁴.

Hazardous compounded sterile preparations must be transported in rigid containers marked "Cytotoxic" and designed to minimize the risk of cracking or failure of the preparation containers. They should not be transported via pneumatic tube systems.

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 hazardous compounded sterile preparations. The sterile compounding supervisor must also ensure that the private carrier knows the procedures to be followed in the event of a spill, that a spill kit is available and that transport personnel have received appropriate training.

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 delivery to the patient.

All personnel involved in transporting hazardous compounded sterile preparations must be trained in the procedures for such transport and for spills or accidental exposure.

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



6.10 Recall of hazardous sterile products or final hazardous 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 hazardous product or preparation does not meet requirements, the pharmacist or pharmacy technician must be able to

- identify patients who have received the hazardous 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 hazardous compounded sterile preparations recorded in the patient's file and the preparation log must be sufficient to allow users to track recipients of hazardous compounded sterile preparations.

The sterile compounding supervisor must ensure that a procedure for recall of hazardous 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

6.11.1 Accidental exposure¹⁴⁵

Policies and procedures to be followed in case of accidental exposure of personnel to hazardous products must be established (*see* Appendix 1). For products with material safety data sheets, those documents must be accessible in the workplace.

If a hazardous product comes into contact with skin or clothing, the person must immediately remove all PPE and contaminated clothing and wash the affected area with plenty of water and soap.

If a hazardous product comes into contact with the eyes, the eyes should be rinsed with water or saline for at least 15 minutes. An appropriate eyewash station must be available for this purpose. Persons wearing contact lenses must remove them promptly after exposure.

In the event of a needle-stick injury involving a hazardous product, bleeding should be induced by massaging toward the wound (without pinching). The area should then be rinsed abundantly with clear water for 5 minutes and then washed with plenty of water and soap¹⁴⁶. A physician should be consulted.

The exposure must be documented in the appropriate logs.

145 Association paritaire pour la santé et la sécurité du travail du secteur affaires sociales (ASSTSAS). Chapter 12: Management of waste, accidental exposure, spills and returns. In: *Prevention guide — safe handling of hazardous drugs*. Montréal, QC: ASSTSAS; 2008. p. 12-5. Available from: <https://www.irsst.qc.ca/media/documents/PublRSST/CG-002.pdf>

146 Association paritaire pour la santé et la sécurité du travail du secteur affaires sociales (ASSTSAS). Chapter 12: Management of waste, accidental exposure, spills and returns. In: *Prevention guide — safe handling of hazardous drugs*. Montréal, QC: ASSTSAS; 2008. p. 12-5. Available from: <https://www.irsst.qc.ca/media/documents/PublRSST/CG-002.pdf>



6.11.2 Spills

Policies and procedures

Policies and procedures for managing spills must be established.

Training and garb

Employees who clean up spills must have received adequate training, must wear appropriate garb while cleaning up a spill and must use a chemical cartridge respirator for organic vapours equipped with a pre-filter. The respirator must be properly fitted to provide maximum protection in the presence of aerosolized or powdered products.

Spill kits

Spill kits must be available in locations where hazardous products are handled and must be present on carts used for transporting hazardous products. The contents of spill kits should be verified regularly and their expiration dates checked. For additional information, please see the *Prevention Guide — Safe Handling of Hazardous Drugs*, published by the ASSTSAS, which describes the content and use of spill kits.

6.11.3 Incidents and accidents

When an incident or accident involving a hazardous 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 Hazardous waste management

In the performance of assigned duties, the pharmacist or pharmacy technician must^{147, 148}

- 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.

Hazardous products must be destroyed in accordance with regulations governing such products¹⁴⁹. A list of hazardous products in use must be available in the pharmacy. The NIOSH list¹⁵⁰ can be used to determine whether a particular product is hazardous.

147 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

148 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>

149 American Society of Health-System Pharmacists. ASHP guidelines on handling hazardous drugs. *Am J Health Syst Pharm*. 2006;63(12):1172-93.

150 National Institute for Occupational Safety and Health (NIOSH). NIOSH list of antineoplastic and other hazardous drugs in healthcare settings 2012. Publ. No. 2012-150. Atlanta, GA: Department of Health and Human Services, Centers for Disease Control and Prevention, NIOSH; 2012 June. Available from: <http://www.cdc.gov/niosh/docs/2012-150/pdfs/2012-150.pdf>



Policies and procedures for the management of hazardous waste¹⁵¹ must be developed and followed. These policies and procedures must comply with local, provincial/territorial and federal requirements and must include the following provisions:

- All personnel involved in the management of hazardous waste must receive appropriate training on destruction procedures to ensure their own protection and to prevent contamination of the premises or the environment¹⁵².
- All equipment, products and vials used in the compounding of hazardous sterile preparations must be discarded in a hazardous waste container.
- Hazardous waste containers must be identified with a self-adhesive label marked “Hazardous waste – cytotoxic”¹⁵³. Containers should be filled to only three-quarters of their capacity¹⁵⁴. Once a bin is three-quarters full, it should be sealed. Personnel should never attempt to compress the contents of a hazardous waste bin.
- Sharps containers removed from the C-PEC must be decontaminated and then discarded into a hazardous waste container and sent for destruction.
- Non-sharps waste used in the compounding of hazardous sterile preparations must be placed in a hazardous waste container inside the C-PEC or placed in a sealable plastic bag before removal from the C-PEC and then discarded in a hazardous waste container.
- Outer gloves must be removed inside the C-PEC. The gloves must be placed in a hazardous waste container inside the C-PEC or placed in a sealable plastic bag before removal from the C-PEC and then discarded in a hazardous waste container.
- All PPE must be discarded in a hazardous waste container.
- Bins used for hazardous waste must comply with local, provincial/territorial and federal requirements. These bins must be incinerated; decontamination by autoclave and subsequent burial is prohibited.

151 Association paritaire pour la santé et la sécurité du travail du secteur affaires sociales (ASSTSAS). Chapter 12: Management of waste, accidental exposure, spills and returns. In: *Prevention guide — safe handling of hazardous drugs*. Montréal, QC: ASSTSAS; 2008. p. 12-2. Available from: <https://www.irsst.qc.ca/media/documents/PublRSST/CG-002.pdf>

152 United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013. p. 369.

153 Association paritaire pour la santé et la sécurité du travail du secteur affaires sociales (ASSTSAS). Chapter 12: Management of waste, accidental exposure, spills and returns. In: *Prevention guide — safe handling of hazardous drugs*. Montréal, QC: ASSTSAS; 2008. p. 12-2. Available from: <https://www.irsst.qc.ca/media/documents/PublRSST/CG-002.pdf>

154 Association paritaire pour la santé et la sécurité du travail du secteur affaires sociales (ASSTSAS). Chapter 12: Management of waste, accidental exposure, spills and returns. In: *Prevention guide — safe handling of hazardous drugs*. Montréal, QC: ASSTSAS; 2008. p. 12-3. Available from: <https://www.irsst.qc.ca/media/documents/PublRSST/CG-002.pdf>



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 hazardous 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 (C-PEC, etc.) attain and maintain the conditions required for contamination-free compounding of hazardous sterile preparations and that hazardous 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 C-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 containment primary engineering control

7.3.2.1 Certification

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

- at least every 6 months¹⁵⁵;
- during installation of new equipment or a new controlled area;
- during maintenance or repair of equipment (repair of C-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 C-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 C-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.

The program should include verification for chemical contamination by hazardous materials on surfaces used for receipt, storage, preparation and verification of products and preparations, in addition to verification of microbiological contamination of controlled areas twice per year.

¹⁵⁵ 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



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;
- 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 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 (BSC, CACI, ACD, etc.) shall be verified 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 C-PEC¹⁵⁶

A written sampling plan for controlled areas and the C-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 and 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.

¹⁵⁶ United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013. pp. 373-5.



Sampling specifications

Samples must be obtained at least every 6 months from the air in controlled areas and in the C-PEC¹⁵⁷ *and* every time that the following conditions are present:

- during installation of new equipment or a new controlled area;
- during maintenance or repair of equipment (repair of C-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 C-PEC certification.

Sampling of non-viable particles in air

Non-viable particles in the air in controlled areas and the C-PEC must be sampled at least every 6 months¹⁵⁸ 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 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);

157 United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013. p. 374.

158 United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013. p. 374.



- 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).

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 retained¹⁵⁹).

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 incubated¹⁶⁰. Tryptic soy agar should be incubated at 30°C to 35°C for 48 to 72 hours. Malt extract agar 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 classification¹⁶¹. 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

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

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

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



- 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

Surface sampling of C-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 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.

Hazardous drug contamination and wipe sampling

Some laboratories offer testing for surface contamination with certain hazardous drugs.

The level of hazardous drug contamination should be measured at least every 6 months¹⁶² or more frequently if any major change is made in placement of furniture, aseptic processes, or cleaning and disinfecting practices.

The sterile compounding supervisor or a delegate should sample the various sites, especially those most likely to be contaminated (e.g., outside the C-PEC, floor surrounding the C-PEC). The sites sampled and the frequency of monitoring should be established on the basis of results obtained on previous monitoring.

A baseline assessment should precede any preventive measure (as described in the ASSTSAS guide¹⁶³), and monitoring should be repeated after implementation of such measures, to determine their effectiveness.

Surface contamination by hazardous antineoplastic drugs, as determined by environmental monitoring, must be recorded in the general maintenance log.

¹⁶² United States Pharmacopeial Convention (USP). General chapter <800>: hazardous drugs — handling in health care settings . Rockville, MD: USP; 2016. p. 90

¹⁶³ 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/PubIRSSST/CG-002.pdf>



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 sampling¹⁶⁴

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 polysorbate¹⁶⁵, 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 removed and discarded, and hand and forearm hygiene must then 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 type of GFS sampling (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.

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–NF¹⁶⁶.

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 there¹⁶⁷.

A tryptic soy agar (low sulphur content) or soybean-casein digest nutrient medium must be used. For hazardous compounded sterile preparations with low or medium risk of microbial contamination, the nutrient medium

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

165 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. p. 900–8.

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

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



must be sterile. For hazardous 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 pharmacy¹⁶⁸.

The containers used for media fill tests should be sent to a certified external laboratory or may be incubated in the pharmacy, provided that the incubator is certified periodically and provided that 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 the 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 days¹⁶⁹. 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 hazardous compounded sterile preparations

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

The program must monitor, among other things,

- the presence of a compounding protocol for each compounded hazardous 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 hazardous compounded sterile preparations log for individual patients and the batch hazardous compounded sterile preparations log, ensuring the performance of all verification steps required during and after compounding.

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 designated in 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.

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

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



All completed documentation concerning components of environmental verification of controlled areas, the C-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 C-PEC must be accessible throughout the entire service life of the facility and the C-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. SOURCES 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.

For more information on compounding of hazardous sterile preparations (handling in health settings), please refer to General Chapter <800> 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/procedures 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 containment primary engineering control, use of aseptic techniques for compounding preparations in the containment 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 containment 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 hazardous 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 ¹⁷⁰ .
Biological safety cabinet (BSC)	Laminar airflow workbench that is ventilated to protect personnel, hazardous compounded sterile preparations and the immediate environment. The open front of a BSC has the following features: <ul style="list-style-type: none"> • air intake, to protect compounding personnel from hazardous sterile preparations; • descending air curtain filtered with a high-efficiency particulate air filter, to protect the hazardous sterile product; • air evacuation system equipped with high-efficiency particulate air filters for environmental protection¹⁷¹.
Cleaning	Removal of dirt, dust and other substances that may host microorganisms ¹⁷² .
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 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.

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

171 Commission de la santé et de la sécurité du travail (CSST). *Material safety data sheet user's guide*. CSST; 2010. Available from: http://www.csst.qc.ca/en/publications/Documents/DC_200_338_6A_web1.pdf

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

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 containment isolator (CACI)	<p>Isolator used specifically for compounding hazardous sterile preparations and designed to protect personnel from any undesirable exposure to airborne medicinal products during compounding and transfer of hazardous material and drugs and to provide an aseptic environment for sterile preparations.</p> <p>The device must not allow any exchange of air between the inside of the clean room and the isolator, unless the air is filtered by a high-efficiency particulate air filter capable of filtering out airborne particles of the drugs being prepared. For the compounding of hazardous preparations, the air exiting the isolator should be evacuated to the building's exterior by an appropriate ventilation system.</p>
Compounding personnel	Pharmacists, pharmacy technicians and/or pharmacy assistants assigned to the compounding of sterile preparations.
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.
Containment primary engineering control (C-PEC)	<p>A device that provides an ISO Class 5 environment for the exposure of critical sites during aseptic compounding and that is designed to minimize airborne contamination of hazardous products, to protect workers and the environment from exposure to hazardous drugs.</p> <p>For compounding of hazardous sterile preparations, C-PECs include biological safety cabinets and compounding aseptic containment isolators.</p>
Contiguous	<p>A term describing a location or space that adjoins another.</p> <p>Example: The clean room is contiguous with the anteroom and the surrounding pharmacy areas.</p> <p>Synonyms: adjacent, adjoining, bordering, abutting, surrounding, neighbouring</p>
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 ¹⁷³ . The clean room and anteroom are examples of controlled areas. Also known as a classified area or room.
Critical area	Work area inside a containment primary engineering control ensuring ISO Class 5 air quality, where 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 ¹⁷⁴ .

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

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



Deactivation	Treatment of a hazardous drug to create a less hazardous agent. One method is chemical deactivation ¹⁷⁵ .
Decontamination	Transfer of a hazardous drug contaminant from a fixed surface (e.g., counter, bag of solution) to a disposable surface (e.g., wipe, cloth). The wipe is then contained and discarded as hazardous waste ¹⁷⁶ .
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 ¹⁷⁷ .
Disinfection	Treatment that eliminates most of the pathogens present on an object or surface ¹⁷⁸ .
Dispensing (of a prescription)	All activities relating 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.
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) ¹⁷⁹ . 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 ¹⁸⁰ . Such drugs are considered hazardous because their effects present risks for personnel ¹⁸¹ .
Hazardous material	A material that, because of its properties, constitutes a danger to an employee's health, safety or physical integrity ¹⁸² . Hazardous materials are dangerous products regulated by a workplace hazardous material information system; as such, they are considered "controlled" products under the Controlled Products Regulations ¹⁸³ .
Hazardous product	A substance that entails 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.

175 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>

176 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>

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

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

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

180 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>

181 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>

182 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>

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



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 ¹⁸⁴ .
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.
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 ¹⁸⁵ .
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.
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 the workers, and be easily and rapidly accessible to those who are likely to come in contact with the product.” ¹⁸⁶ 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 ^{187, 188} .
Multiple-dose container	Commercial drug container in multiple-dose format for parenteral administration only. The product usually contains an antimicrobial preservative ¹⁸⁹ .
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 ^{190, 191} .
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.

184 Commission de la santé et de la sécurité du travail (CSST). *Material safety data sheet user's guide*. CSST; 2010. Available from: http://www.csst.qc.ca/en/publications/Documents/DC_200_338_6A_web1.pdf

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

186 Commission de la santé et de la sécurité du travail (CSST). *Material safety data sheet user's guide*. CSST; 2010. Available from: http://www.csst.qc.ca/en/publications/Documents/DC_200_338_6A_web1.pdf

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

188 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>

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

190 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/PubIRSSST/CG-002.pdf>

191 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>



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.
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 adopt 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).
Single-dose vial	Single-dose commercial container corresponding to a fixed dose of a drug intended for parenteral administration only ¹⁹² . Labelled 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 pharmacist 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 ¹⁹³ .
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.

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

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



10. LIST OF TABLES

Table 1	Classes of air cleanliness for airborne particulates in clean rooms and clean areas, according to ISO 14644-1
Table 2	Functional parameters of the clean room and anteroom for the compounding of hazardous sterile preparations
Table 3	Requirements for a hazardous products storage area
Table 4	Functional parameters of a shared anteroom for the compounding of hazardous and non-hazardous sterile preparations
Table 5	Masks and chemical cartridge respirators
Table 6	Contamination risk levels
Table 7	Beyond-use dates (BUDs) for hazardous compounded sterile preparations, according to risk of microbial contamination
Table 8	Minimum frequency of surface decontamination, deactivation and disinfection of the inside of a biological safety cabinet (BSC) or compounding aseptic containment isolator (CACI)



11. APPENDICES

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

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 competency assessment program, including details of compounding hazardous products		
2.2	Program to assess maintenance of competency, including the characteristics of compounding hazardous sterile preparations		
2.3	Training and assessment of cleaning and disinfecting personnel, including cleaning in the context of compounding hazardous sterile preparations		
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	Facilities and equipment necessary for the compounding of hazardous sterile preparations		
4.3	Reservation of facilities and equipment for the compounding of hazardous sterile preparations		
4.4	Maintenance of facilities and equipment, taking into account the characteristics of compounding hazardous sterile preparations (e.g., certification of rooms and devices, calibration, maintenance of pre-filters and high-efficiency particulate air filters, verification of pressure)		
4.5	Cleaning and disinfecting activities for facilities and equipment		
B	COMPOUNDED STERILE PREPARATIONS		
1.	Receiving and unpacking of hazardous sterile products		
2.	Storage of hazardous sterile products		
3.	Determining beyond-use dates of products used in a preparation		
4.	Determining beyond-use dates of final preparations		
5.	Hand and forearm hygiene		
6.	Garbing in compounding areas and for compounding		
7.	Bringing equipment and products into the clean room and containment primary engineering control		
8.	Verification of the compounding process (including validation of calculations by a pharmacist) and of final preparations		
9.	Decontamination, deactivation and disinfection of the containment primary engineering control		
10.	Aseptic techniques for compounding hazardous sterile preparations		



	11.	Packaging of final hazardous compounded sterile preparations	
	12.	Labelling of final hazardous compounded sterile preparations	
	13.	Storage of final hazardous compounded sterile preparations	
	14.	Recording of preparations in the patient file	
	15.	Transport and delivery of final hazardous compounded sterile preparations (to the patient, to patient care units or to the dispensing pharmacist)	
	16.	Hazardous waste management (e.g., at the pharmacy, returns from patients or patient care units, instructions to patients)	
	17.	Accidental exposure of personnel to hazardous products (e.g., eyewash station, log)	
	18.	Spills (e.g., spill management, use of chemical cartridge respirator, kit)	
	19.	Recall of hazardous products or final hazardous compounded sterile preparations	
C		QUALITY ASSURANCE PROGRAM	
	1.	Verification and maintenance of equipment	
	2.	Environmental control of facilities and containment 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)	
D		ENVIRONMENTAL MONITORING PROGRAM	
	1.	Environmental monitoring for chemical contamination	



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
- 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>
- National Institute for Occupational Safety and Health (NIOSH). NIOSH list of antineoplastic and other hazardous drugs in healthcare settings 2012. Publ. No. 2012-150. Atlanta (GA): Department of Health and Human Services, Centers for Disease Control and Prevention, NIOSH; June 2012. Available from: <http://www.cdc.gov/niosh/docs/2012-150/pdfs/2012-150.pdf>
- 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 and General Chapter <800> Hazardous drugs - handling in healthcare settings).

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>
- Canadian Society of Hospital Pharmacists, compounding-guidelines for pharmacies, 2014.
- 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, Pruemer 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	PH	PT	PA
1.	FOR THE COMPOUNDING OF HAZARDOUS STERILE PREPARATIONS			
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, deactivation and decontamination 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 containment 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 HAZARDOUS STERILE PREPARATIONS			
2.1	Have the competency required to compound sterile preparations.	X	X	X
2.2	Identify hazardous products in the composition of sterile preparations.	X	X	X
2.3	Know and apply deactivation and decontamination measures.	X	X	X
2.4	Know and use the protection measures necessary to avoid exposure to hazardous substances.	X	X	X
2.5	Know and use personal protective equipment specifically for handling hazardous products and preparations.	X	X	X
2.6	Safely handle hazardous products during receipt, unpacking, storage and delivery.	X	X	X
2.7	Know and use the appropriate aseptic technique for hazardous products in the workplace.	X	X	X
2.8	Know and use the emergency measures to be applied in the case of accidental exposure, accidents or spills.	X	X	X
2.9	Know how to safely destroy hazardous products and the materials used in their preparation.	X	X	X
3.	FOR THE COMPOUNDING OF HIGH-RISK HAZARDOUS STERILE PREPARATIONS (MADE WITH NON-STERILE PRODUCTS)			
3.1	Have the competency required to compound sterile preparations.	X	X	X
3.2	Know and correctly perform sterilization by filtration.	X	X	X
3.3	Know and correctly perform the filter integrity verification.	X	X	X
3.4	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 AREA USED FOR COMPOUNDING HAZARDOUS STERILE PREPARATIONS			
1.1	Know, correctly perform and document cleaning and disinfecting tasks for the general area for compounding of hazardous sterile preparations.	X	X	X
1.2	Know and use personal protective equipment specifically for handling hazardous products and preparations.	X	X	X
1.3	Know and use the emergency measures to be applied in case of accidental exposure, accidents or spills.	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 _____ (dd/mm/yyyy) Effective date: _____ (dd/mm/yyyy)
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 CONTAINMENT PRIMARY ENGINEERING CONTROLS

Note: The following appendix lists the responsibilities of the certifier, a person engaged to certify sterile-product compounding rooms and the containment primary engineering control (C-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.

<p>1. Before certification visit</p> <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., C-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. 	
<p>2. General precertification requirements</p> <ul style="list-style-type: none"> ▪ Cleans and disinfects all equipment brought into the controlled rooms. ▪ Performs certification of the controlled rooms and C-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. ▪ Is familiar with the products used, especially if they are hazardous. ▪ Does not touch hazardous products. If touching a hazardous product is required, asks qualified personnel to do so. ▪ If applicable, sets up a protective wall (plastic or other) before opening the device, to limit contamination of the controlled room by hazardous products. ▪ Performs the work meticulously and professionally. 	
<p>3. Certification steps, directed by CETA application guides CAG-002, CAG-003 and CAG-008</p>	
<p>3.1 Certification of controlled areas</p>	
<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.* 	



<ul style="list-style-type: none"> ▪ 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>	
<p>3.2 Certification of BSC</p>	
<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). 	
<p>3.3 Certification of CACI</p>	
<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 	
<p>4. After certification</p>	
<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. ▪ Groups all waste contaminated by hazardous products and disposes of it as hazardous waste in the appropriate containers. ▪ 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 AND BIOLOGICAL SAFETY CABINETS

TARGET	CERTIFICATION STANDARDS	CERTIFICATIONS
<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><u>Class II, type B2 BSC certification includes steps carried out 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; count of non-viable particles in 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 containment isolator</p>	<ul style="list-style-type: none"> • CETA CAG-002-2006: Compounding Isolator Testing Guide 	<p><u>Isolator certification includes steps carried out 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 • 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 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
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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; LAFW = laminar airflow workbench; NEBB = National Environmental Balancing Bureau; NSF = NSF International (public health and safety organization).

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 hazardous 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 hazardous 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 hazardous compounded sterile preparation will be presented to the patient.

Stability and storage

Specify the preservation requirements of the hazardous compounded sterile preparation.

Specify the shelf life of the hazardous 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 hazardous 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 hazardous 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

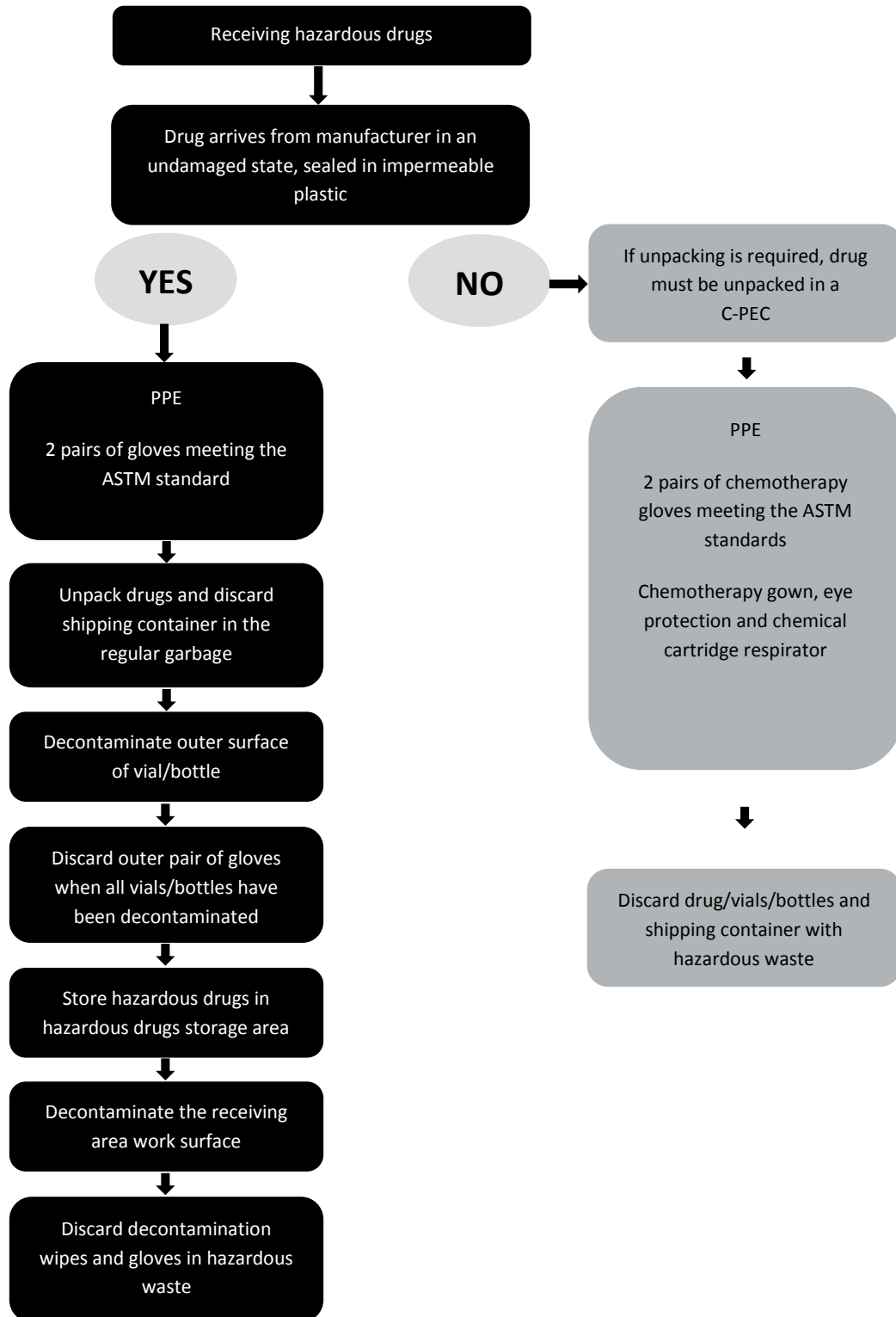
Packaging or system used	Examples
Ophthalmic drops	50 mg/mL vancomycin ophthalmic solution prepared from a 500-mg vial. The vehicle used and product taken from the vial must be checked before insertion into the dispenser bottle.
Diluted cassette	50 mg/mL Morphine-HP® in a 10-mL vial diluted to a final 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 PROCEDURE EXAMPLE

Receiving, unpacking and storing hazardous products

(refer to section 6.8 for details)



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 is 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 Pressure differential between controlled areas	<ul style="list-style-type: none"> • Once a day • 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 C-PECs	<ul style="list-style-type: none"> • Before first use • Every 6 months • When new C-PEC is installed • When C-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 C-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 C-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 C-PEC is installed • When the C-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 six 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
C-PEC = containment primary engineering control.		



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Note to readers: The references cited in these Model Standards reflect the references appearing in the source document, “Préparation de produits stériles dangereux en pharmacie – Norme 2014.02,” published by the Ordre des pharmaciens du Québec, 2014. Where possible, certain details have been verified against the source documents. URLs for online documents are current as of February 2016.

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