# Model Standards for Pharmacy Compounding of Hazardous Sterile Preparations

## DRAFT 4

**National Association of Pharmacy Regulatory Authorities**
**(adapted with permission from "Préparation de produits stériles dangereux en pharmacie – Norme 2014.02," Ordre des pharmaciens du Québec, 2014)**

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## CONTENTS

# 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[1].

Evolving practice and increased awareness of the inherent dangers of compounding sterile preparations for the health of both patients and compounding personnel[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 Quebec, which are in turn based on General Chapter <797> of the United States Pharmacopeia – National Formulary (USP–NF) in effect in the United States since 2004. Their preparation was led by the NAPRA ad hoc Committee on Pharmacy Compounding and involved extensive consultations with experts and stakeholders.

# 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 the Model Standards of Practice for Canadian Pharmacists and Pharmacy technicians as well as other policies and guidelines that may be in place in provincial/territorial jurisdictions.

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[1] Dolan SA, Felizardo G, Barnes S, Cox TR, Patrick M, Ward KS, et al. APIC position paper: safe injection, infusion, and medication vial practices in health care. *Am J Infect Control.* 2010:38(3):167-72.

[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 Pham Compound.* 2002;6(6):404-7.

# 3. REGULATORY FRAMEWORK

Many health care professionals prepare compounded sterile preparations, 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 medication (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"[5]. 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.

The NAPRA 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 and scope of practice. Therefore, individuals who do not have the knowledge, training, expertise, facilities or equipment required to compound sterile preparations 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 preparation for them.

Compounded sterile preparations include the following types of medications:

- nasal inhalation solutions
- respiratory therapy solutions

[5] 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

- 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 and abdominal pelvic)
- ophthalmic drops and ointments
- otic drops for intratympanic administration
- parenteral nutrition
- dialysis solutions
- allergen extracts
- topical preparations (where sterility is essential to therapy)
- 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 within the province of Quebec |
| BUD | Beyond-use date |
| BSC | Biological safety cabinet |
| CACI | Compounding aseptic containment isolator |
| 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 |
| LAFW | Laminar airflow workbench |
| NF | National Formulary (United States) |
| NIOSH | National Institute for Occupational Safety and Health (United States) |
| PPE | Personal protective equipment |
| PA | Pharmacy assistant |
| PT | Pharmacy technician |
| 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 the implementation of 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 penetration[6].

Absorption through the skin occurs by direct contact with contaminated surfaces or objects. Ingestion occurs by eating foods that might have been contaminated or by putting contaminated hands or objects, particularly pens, into the mouth[7] [8]. Inhalation of vapourized drugs can also be a source of contamination[9].

References on the safe handling of hazardous products must be consulted before compounding services for such products are implemented. Additional laws and regulations governing the compounding of hazardous sterile preparations and other

[6] American Society of Health-System Pharmacists. ASHP guidelines on handling hazardous drugs. *Am J Health Syst Pharm*. 2006;63(12):1172-93.
[7] American Society of Health-System Pharmacists. ASHP guidelines on handling hazardous drugs. *Am J Health Syst Pharm*. 2006;63(12):1172-93.
[8] 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: http://www.asstsas.qc.ca/publications/publications-specialisees/guides-de-prevention/prevention-guide-safe-handling-of-hazardous-drugs.html
[9] American Society of Health-System Pharmacists. ASHP guidelines on handling hazardous drugs. *Am J Health Syst Pharm*. 2006;63(12):1172-93.

hazardous materials may exist at the federal/provincial/territorial level and would need to be consulted.

## 5.1 Personnel

### 5.1.1 Roles and responsibilities

#### 5.1.1.1 Pharmacy manager[10] or pharmacy department head[11]

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 for these activities. 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 sterile compounding supervisor and must be qualified to prepare hazardous compounded sterile preparations in the pharmacy.

If these responsibilities are assigned to pharmacist or a 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 committee[12] 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.

#### 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.

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[10] In the context of this document, a pharmacy manager will be the pharmacist who owns the pharmacy in the province of Québec and the pharmacist designated as the manager by the pharmacy owner and/or recognized as the manager by the provincial/territorial regulatory authorities in other Canadian jurisdictions.

[11] In the context of this document, the pharmacy department head is a pharmacist who is licensed with the provincial/territorial pharmacy regulatory authorities to practice pharmacy.

[12] 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: http://www.asstsas.qc.ca/publications/publications-specialisees/guides-de-prevention/prevention-guide-safe-handling-of-hazardous-drugs.html

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

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(PA) with the appropriate training[13], utilizing a delegation process from the pharmacist as applicable by the provincial/territorial requirements.

**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 and updated (at least every 3 years or more frequently when standards change) 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 manufacturer's specifications or standards, whichever is more stringent.
- The existing compounding process yields high-quality sterile preparations that are safe for patients.
- 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.

[13] Please consult the provincial/territorial pharmacy regulatory authorities as training requirements may be defined

#### 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 sterile compounded preparation whether working in the same or different facilities/pharmacies, responsibilities towards the patient are shared between them. In such instances, all parties must comply with provincial/territorial requirements and standards regardinginter and intra-professional collaboration.

b) A pharmacy assistant with the appropriate training[14], assigned to prepare sterile preparations or perform other technical tasks related to sterile compounding only when assigned to do so by the sterile compounding supervisor and after successfully completing a delegation process from a pharmacist as applicable by provincial/territorial requirements

**Responsibilities**

a) 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 aseptic, hygienic, cleanliness and safety rules;
- 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 or digitized;
- ensure that the equipment, instruments and space used are properly cleaned and maintained;
- ensure application of and compliance with existing compounding procedures;

[14] Please consult the provincial/territorial pharmacy regulatory authorities as training requirements may be defined.

- 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 the preparation to be produced;
- follow the compounding process defined in the compounding protocol;
- perform verification during the various stages of compounding and verify the final preparation;
- ensure that all required verification and quality control measures are performed to ensure 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);
- where appropriate, provide, orally and in writing, the pharmacist/pharmacy technician at the facility/pharmacy where the preparation will be dispensed, with the information required for storing and transporting any medication prepared on their behalf for a specific patient (storage method, precautions, suggested BUD, etc.);
- 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);
- where appropriate, notify the pharmacist/pharmacy technician at the pharmacy/facility where the product was dispensed when a preparation must be recalled;

- Prior to dispensing or releasing the medication to the patient ensure that all standards of practice associated with dispensing a prescription are 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 occurs between the pharmacists and pharmacy technicians at each facility to clarify who is responsible for which aspects of patient care and to ensure continuity of care[15].

[15] 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

b) The responsibilities of the pharmacy assistant assigned to prepare sterile preparations or perform other technical tasks related to sterile preparations compounding are determined at the discretion of the sterile compounding supervisor. The sterile compounding supervisor should only assign tasks which are permitted by provincial/territorial legislation and for which the pharmacy assistant has the appropriate training. 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[16,17] are therefore required.

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

Compounding personnel must keep their compounding knowledge and skills up to date.

#### 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 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 successfully 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 hazardous sterile preparation compounding.

[16] 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.

[17] 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.

The assessment results and any corrective measures imposed must be recorded, and these records must be retained as required by 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 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. Personnel must pass GFS and media fill test before working in the hazardous sterile compounding area.

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 in cleaning and disinfecting personnel training);
- 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) entering the sterile compounding area or involved in sterile compounding must be adequately trained and must follow and comply with specific policies and procedures. This would include contractors, volunteers, employees, students, interns, equipment maintenance personnel or others.

#### 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 must have demonstrated the required competencies.
- The sterile compounding supervisor must also have the competency required to manage a safe, high quality hazardous sterile-preparation compounding area.

Assessment

- The sterile compounding supervisor must be evaluated at the same frequency as for the compounding personnel by a third party 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.

**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 element to cover as part of the 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 must be retained for the period specified by the 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 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, demonstrated ability to determine whether

the pharmacy technicians and pharmacy assistants are complying with aseptic processes, in order to quickly detect any risk of error and possible contamination;

- must pass the practical section of the training program regarding assessment of the aseptic compounding process, the media fill test and GFS, if there is a possibility that this pharmacist will compound hazardous sterile preparations on an occasional basis.

**Pharmacist on duty in a health care facility**

A pharmacist on duty in a health care facility where a pharmacist will be expected to compound sterile preparations, must receive the same training as a compounding pharmacist and must undergo annual assessment of competency in 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, but must 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, certification that competencies in this area are being maintained and developed;
- the third party evaluator's annual competency assessment must include

the same elements as the competency assessment program for compounding personnel as described in section 5.1.2.3 above.

The third party evaluator can perform the training and assessment at the workplace but also, at an alternate location. Independent of the location where the training and assessment are performed, the third party evaluator must evaluate specific workplace policies and procedures.

## 5.2 Policies and procedures[18,19]

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/pharmacy technician where the dispensing took place should include in their general procedures information about policies and procedures for acquiring compounded sterile preparations for their patients (originating pharmacy entry in the file, delivery, etc.)

## 5.3 Facilities and equipment[20]

Facility design (spaces, ventilation, materials, etc.), as well as the conduct and competency of personnel, helps to achieve the objectives of these Model Standards.

Facilities for the compounding of hazardous sterile preparations must be designed and

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

[19] Pharmacy Compounding Accreditation Board (PCAB). Standard 1.40: Standard operating procedures compliance indicators. In: *PCAB accreditation manual.* Washington, DC: PCAB; 2011. p. 7. Available from: http://www.pcab.org/cms/wp-content/themes/pcab/img/PCAB-Accreditation-Manual.pdf

[20] 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: http://www.asstsas.qc.ca/publications/publications-specialisees/guides-de-prevention/prevention-guide-safe-handling-of-hazardous-drugs.html

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 government buildings.

### 5.3.1 Useful references

#### 5.3.1.1 ISO Standard 14644-1[21]

The ISO 14644-1 classification describes air cleanliness requirements in facilities and clean rooms. This standard specifies the allowable concentration of airborne particles for each class (Table 1). To achieve and maintain the ISO class for a clean room, all sources that generate particles must be controlled.

**Table 1**

| **Classes of air cleanliness for airborne particulates in clean rooms and clean areas, according to ISO 14644-1** | |
|---|---|
| ***ISO Class Number*** | ***Maximum concentration of non-viable particles ≥ 0.5 µm 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 |
| **µm = micrometre; $m^3$ = cubic metre; ISO = International Organization for Standardization** | |

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

#### 5.3.1.2 Prevention Guide — Safe Handling of Hazardous Drugs[22]

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 "definitely apply to all antineoplastic drugs, whether used in oncology or to treat other illnesses (e.g. methotrexate for arthritis). However, certain precautions could be modulated for other categories depending on the specific risks of each category"[23].

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

#### 5.3.1.3 NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings[24]

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 products. This published list can be used by individual pharmacies to develop their own lists of hazardous products that require special handling precautions. A list of hazardous products used must be available at the pharmacy. Each of these products needs to be handled and disposed of properly.

In addition, NIOSH published an alert on preventing occupational exposure to antineoplastic and other hazardous drugs in 2004[25].

### 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

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[22] 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: http://www.asstsas.qc.ca/publications/publications-specialisees/guides-de-prevention/prevention-guide-safe-handling-of-hazardous-drugs.html

[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: http://www.asstsas.qc.ca/publications/publications-specialisees/guides-de-prevention/prevention-guide-safe-handling-of-hazardous-drugs.html

[24] 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

[25] 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

requirements are similar for the two types of preparations. This document describes the facilities required for the compounding of 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 to minimize both the risk of airborne contamination in controlled rooms used for the compounding of hazardous sterile preparations and to minimize the exposure to hazardous products in the work environment. It must also be designed to achieve and maintain an ISO class 7 air quality for clean rooms and anterooms used for the compounding of hazardous sterile preparations[26] (*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 particular air (HEPA) filter to ensure a very high level of cleanliness. The supply air must come from the ceiling via diffusers, each fitted with a terminal HEPA filter[27].

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 preparations[28].

The air quality in controlled rooms must comply with the ISO 14644-1, according to the specifications listed in Table 1, under dynamic operating conditions, as follows:

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

[27] 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

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

- The number of particles ≥ 0.5 µm diameter per cubic metre of air must be verified while compounding personnel perform or simulate a typical compounded sterile preparation.
- An example of a simulation of a typical sterile preparation is a media fill.

The particle count must be performed by trained, qualified personnel at least every 6 months as part of an internal quality control program for facilities and containment primary engineering controls (C-PECs) (ex. 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*).*

All of the air from the clean room and anteroom must be exhausted to the exterior of the building.

Exhaust air intakes must be installed at the bottom of the walls[29], 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 exhaust air intake 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 facilities must have at least two separate controlled rooms, enclosed and physically separated by a wall: a clean room, where the containment primary engineering control (e.g., BSC or CACI) is located, and an anteroom, located next to the clean room.

See also section 5.3.2.6

**<u>Clean room</u>**

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

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

(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 room[30] 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 for the compounding of hazardous sterile preparations.

Contents

The containment primary engineering control (C-PEC) is installed in the clean room. For hazardous compounding, the containment primary engineering controls includes BSCs or CACIs[31].

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 drugs and the refrigerator in which they are stored may be placed in the clean room for compounding sterile hazardous 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 that there are sufficient ACPHs to maintain an ISO class 7 clean room. The use of equipment in the clean room is permitted as long as their use and performance has no negative impact on the viable and non-viable performance of the clean room.

## Anteroom[32]

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

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

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

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

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

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

- 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. Even though this area is referred to as "dirty," it is considered to be chemically clean 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. Even though this area is referred to as "clean," it is considered to be chemically contaminated when hazardous preparations are being compounded in the clean room.

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

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 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 6.6.2.2 for garbing and 5.3.3.3 for PPE);
- 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 with persistent activity and it's dispenser;
- hand-drying system:
  - lint-free towels with a dispenser (preferred)
  - 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 station[33], if available (if not located in the anteroom, the eyewash station must be installed nearby).
- pass-through for transferring products into the clean room and/or a cart reserved for use in the "clean" area of the anteroom and the clean room.

Supplies

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.

The anteroom has two doors; one door between the clean room and anteroom. Another door between the anteroom and the non-controlled area. The pharmacy must have a process whereby only one door is open at one time. Both doors cannot be opened at the same time.

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

Because horizontal surfaces require daily cleaning, their presence in the anteroom must be kept to a minimum, to avoid unduly increasing the workload for cleaning and disinfecting personnel.

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

[33] 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

**Table 2**

| Functional parameters of the clean room and anteroom for the compounding of hazardous sterile preparations |
|---|
| **General principles:**<br>• Maintain negative pressure to prevent air that might become contaminated by hazardous products from leaving the clean room (principle of containment).<br>• Ensure that construction quality is sufficient to guarantee that controlled rooms (i.e., rooms responsible for containment) are airtight.<br>• Notwithstanding the two previous 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).<br>• Maintain ISO Class 7 air quality (to prevent particles from entering the clean room).<br>• Protect the handler (by means of air exhausts).<br>***To adhere to these principles, the following functional parameters must be met:***<br>• The clean room must be kept under negative pressure relative to the anteroom[34].<br>• The pressure of the clean room must be –2.5 Pa relative to surrounding areas (pharmacy or other)[35].<br>• The pressure differential between the anteroom and the clean room ($P_B$ – $P_C$) must be at least 2.5 Pa to maintain unidirectional airflow from the anteroom to the clean room.<br>• 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.<br>• ISO Class 7 air quality must be maintained in the clean room and the anteroom under dynamic operating conditions[36].<br>• There must be at least 30 or more air changes per hour (ACPH)[37] 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.<br>• The temperature in the controlled rooms must be less than or equal to 20°C[38], taking into account employees' comfort once all clean room garb (including PPE) has been donned. Medication storage temperatures must not exceed 25°C.<br>Note: There is no requirement for relative humidity; refer to the recommendations of the Canadian Society of Hospital Pharmacists[39]. See also the pressure diagram for the anteroom and the clean room (Figure 1, page 27). |

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

[35] United States Pharmacopeial Convention (USP). General chapter <800>: hazardous drugs — handling in health care settings [draft]. Rockville, MD: USP; 2014 Mar.

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

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

[38] United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013. <<Should a specific page be indicated for this reference?>>

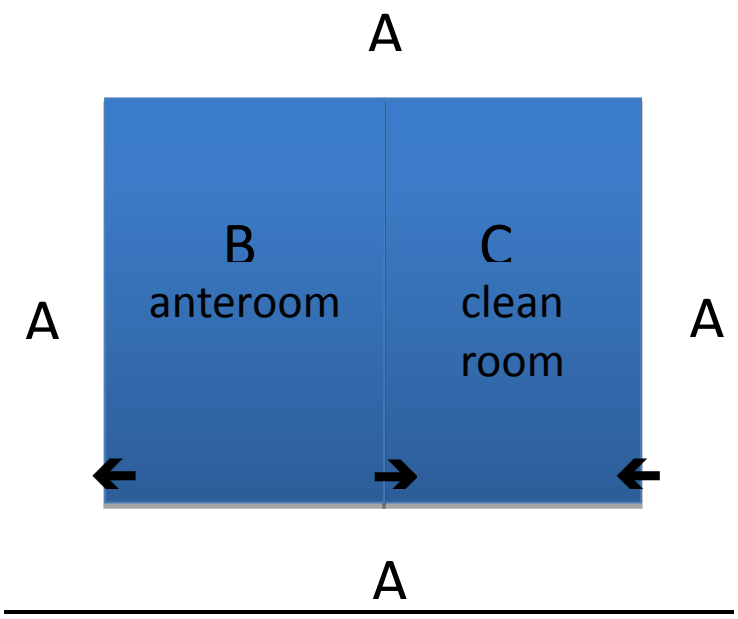
[39] Canadian Society of Hospital Pharmacists (CSHP). Compounding: guidelines for pharmacies. Page 52, Ottawa, ON: CSHP; 2014.

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 supervision and verification activities, one or more observation windows must be installed. Such windows reduce the number of times individuals need to enter and exit the clean room, especially visitors or observers. They also ensure the safety of compounding and other personnel.

**Figure 1: Pressure diagram**




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

## 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 necessary[40].

If a hazardous drug arrives in a damaged state and unpacking is required, a Class I BSC will be needed. The Class I BSC may be used just for unpacking the damaged product, or it could also be used for the compounding of non-sterile hazardous preparations[41].

## Area for storing hazardous products

Hazardous products must be grouped and stored in a properly ventilated room with all air exhausted to the exterior[42]. 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 products[43].

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 sterile hazardous 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 that there are sufficient ACPHs to maintain an ISO class 7 clean room.

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[40] United States Pharmacopeial Convention (USP). General chapter <800>: hazardous drugs — handling in health care settings [draft]. Rockville, MD: USP; 2014 Mar.

[41] United States Pharmacopeial Convention (USP). General chapter <800>: hazardous drugs — handling in health care settings [draft]. Rockville, MD: USP; 2014 Mar.

[42] 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. p. 6-4. Available from: http://www.asstsas.qc.ca/publications/publications-specialisees/guides-de-prevention/prevention-guide-safe-handling-of-hazardous-drugs.html

[43] Association paritaire pour la santé et la sécurité du travail du secteur affaires sociales (ASSTSAS). Chapter 4: General Preventive Measures. *Prevention guide — safe handling of hazardous drugs.* Montréal, QC: ASSTSAS; 2008. pp. 4-4. Available from: http://www.asstsas.qc.ca/publications/publications-specialisees/guides-de-prevention/prevention-guide-safe-handling-of-hazardous-drugs.html

**Table 3**

| Required conditions for a hazardous products storage area |
| --- |
| • Area separate from the unpacking area<br>• Dedicated room<br>• Negative pressure -2.5 Pa relative to surrounding areas<br>• At least 12 air changes per hour (ACPH) with all air exhausted to the exterior<br>• Presence of shelves with lips to prevent drug containers from falling off and breaking[44]<br>• Storage spaces for hazardous products and preparations identified with the proper signage to indicate the presence of hazardous products[45]<br>• Sufficient ventilation to prevent contamination from spreading to adjoining rooms[46] |

A facility may choose to construct a separate room for the storage of hazardous products. However, the storage of sterile hazardous products is permitted in the clean room (see the section on clean rooms 5.3.2, above, for more information).

#### 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 sterile hazardous preparations and another for the

[44] 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. p. 6-4. Available from: http://www.asstsas.qc.ca/publications/publications-specialisees/guides-de-prevention/prevention-guide-safe-handling-of-hazardous-drugs.html

[45] Association paritaire pour la santé et la sécurité du travail du secteur affaires sociales (ASSTSAS). Chapter 4: General Preventive Measures. *Prevention guide — safe handling of hazardous drugs.* Montréal, QC: ASSTSAS; 2008. pp. 4-4. Available from: http://www.asstsas.qc.ca/publications/publications-specialisees/guides-de-prevention/prevention-guide-safe-handling-of-hazardous-drugs.html

[46] 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. p. 7-9. Available from: http://www.asstsas.qc.ca/publications/publications-specialisees/guides-de-prevention/prevention-guide-safe-handling-of-hazardous-drugs.html

compounding of sterile non-hazardous preparations, as well an anteroom for each type of compounding.

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 another for non-hazardous sterile preparations), there may be only one (shared) 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 the Model Standards for Pharmacy Compounding of Non-hazardous Sterile Preparations (section 5.3.2.5).

**Clean room for the compounding of hazardous sterile preparations**

The functional parameters of the clean room for this type of facility are the same as those required for the compounding clean room described in 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 both clean rooms. The functional parameters of the shared anteroom for the compounding of hazardous and non-hazardous sterile preparations are explained in Table 4.

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

- a space or area referred to as “dirty,” located adjacent to the non-controlled area, 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 “ 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 removing PPE. If the anteroom is shared, this area is limited to hand hygiene and donning of PPE. No drugs are stored in the 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:***<br>• The anteroom must be kept under positive pressure relative to the hazardous compounding clean room and non-controlled area<br>• The pressure differential must be at least 5.0 Pa[47] (equivalent to 0.02 inches water column) relative to the adjacent area.<br>• ISO Class 7 air quality must be maintained in the anteroom under dynamic operating conditions[48]. ;<br>• There must be at least 30 air changes per hour (ACPH)[49]. Depending on the size of the room and the number of people working in it, a greater number of ACPH may be required;<br>• 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. |
| |

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 United States Pharmacopeia – National Formulary (USP–NF)[50] for hazardous and non-hazardous sterile preparation compounding rooms.

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

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

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

[50] United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding – sterile preparations. In: *USP pharmacists’ pharmacopeia*. 2nd ed., Suppl. 2. Rockville, MD: USP; 2008. pp. 372 and 373.

#### 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, 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 prevent microorganisms and non-viable contaminants from accumulating.

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

**Ceilings**

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

Ceilings must be constructed of smooth, non-friable, impervious, 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 accumulate[51]. This could 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 installed[52], 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 frame[53]. The tiles on this type of ceiling require periodic preventive sealing because the sealer eventually dries. When facilities undergo certification, this type of ceiling must be tested for tightness. This type of ceiling is not recommended for new facilities.

In all rooms reserved for the compounding of sterile preparations, any holes, cracks or breakage in ceilings must be repaired and sealed at the earliest opportunity.

**Walls**

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

The walls must be constructed of smooth, non-friable, impervious, 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

[51] 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

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

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

panels. All joints must be sealed. In locations at higher risk of breakage, stainless steel 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 non-porous, non-friable, flat, smooth, 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 4-6".

There must be no carpets, rugs, "sticky mats" or anti-fatigue mats.[54].

### 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.

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.

[54] 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

BSCs and CACIs must be connected to a notification system[55] 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, non-porous, non-friable and impervious 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.

A horizontal surface such as a shelf or a cart for donning gloves should be in the clean room.

**Furniture**

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

All furniture must be cleaned and disinfected before being placed in the clean room.

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

**Pass-through and/or cart**

A pass-through, with or without ventilation, 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 products.

It is recommended that the pass-through be equipped with an interlocking system that prevents both doors from being open at once. Otherwise, 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.

[55] 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

#### 5.3.2.11 Signage

Each room must be identified with appropriate and informative signs (example; pictograms indicating cytotoxicity, the need for special care, hazards, restricted access, dress code, etc.).

#### 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 condition 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 replaced as recommended by the manufacturer.

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

### 5.3.3 Equipment

#### 5.3.3.1 Containment Primary Engineering Control(C-PEC)

Hazardous sterile preparations must be compounded inside a C-PEC. Examples of C-PECs for hazardous sterile preparations include Class II or Class III BSC or CACI[56]. Oncology support treatments can also be prepared in these devices, if they are being compounded for the same patient.

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 air quality must comply with ISO Class 5. The HEPA air filter of a C-PEC must be fully exhausted to the exterior of the building.

Before a C-PEC is used,

[56] United States Pharmacopeial Convention (USP). General chapter <800>: hazardous drugs — handling in health care settings [draft]. Rockville, MD: USP; 2014 Mar.

- 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.

The sterile compounding supervisor must ensure that the certification is completed according to certification standards currently in force (*see* Appendix 7).

A C-PEC must operate continuously, 24 hours a day[57]. 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 cleaning, disinfection, decontamination and compounding of hazardous sterile preparations is undertaken[58].

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

The work surface of the C-PEC must be resistant to damage from cleaning, disinfecting, deactiving and decontamination and must be changed if it is 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 C-PEC and other furniture**

The C-PEC and other pieces of furniture should be positioned to avoid interfering with facility ventilation systems[59 60 61].

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 m[62]). Some types of BSC can be built into the wall and sealed or wall-mounted and sealed, but this is not possible with other types. When positioning a C-PEC, the manufacturer's recommendations must be strictly followed to avoid interfering with normal

[57] 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

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

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

[60] 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.

[61] 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

[62] 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. p. 7-9. Available from: http://www.asstsas.qc.ca/publications/publications-specialisees/guides-de-prevention/prevention-guide-safe-handling-of-hazardous-drugs.html

operation. A smoke test may be used to validate proper operation during certification.

BSC[63]

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

CACI[64]

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 the following conditions are met:

1. The room has negative pressure (at least 2.5 Pa negative pressures relative to adjacent spaces)[65].
2. The room has at least 12 ACPH[66].
3. The CACI maintains an ISO Class 5 environment (see Table 1) at all times during compounding, including during the transfer of ingredients, equipment and devices into and out of the CACI.
4. 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.
5. 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 (recovery time).

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

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

[65] United States Pharmacopeial Convention (USP). General chapter <800>: hazardous drugs — handling in health care settings [draft]. Rockville, MD: USP; 2014 Mar.

[66] United States Pharmacopeial Convention (USP). General chapter <800>: hazardous drugs — handling in health care settings [draft]. Rockville, MD: USP; 2014 Mar.

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

**Maintenance of C-PEC**

C-PECs must be maintained in accordance with the manufacturer's recommendations.

BSCs and CACIs must be certified[67]

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

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

HEPA filters should 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 equipment maintenance for C-PECs must be performed when no compounding is in progress, before cleaning and disinfection operations.

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

The sterile compounding supervisor must ensure that C-PEC maintenance has 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. 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 and surface sampling, etc.)[68]. The use of equipment and supplies in the

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

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

clean room and the ante room is permitted as long as their use and performance has no negative impact on the non-viable and viable performance of the rooms.

All necessary devices, instruments and accessories must be cleaned and disinfected before being placed in a controlled area[69]. 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 containment primary engineering control 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 , 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 in some form of documentation (e.g. Mix Check report) for each batch, at a minimum.

**Carts**

If carts are used, one cart must be reserved for the "dirty" area of the anteroom and must remain there[70].

A second cart must be reserved for use in the "clean" area of the anteroom and in the clean room[71].

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

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

[69] United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013. p. 373.
[70] United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013. p. 379.
[71] United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013. p. 379.

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.

Carts should be made of stainless steel or very good quality plastic, should be smooth, non-friable, non-porous and resistant to 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.[72,73] [74] Domestic refrigerators and freezers must not be used.

Use and placement

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

Refrigerators and freezers used to store hazardous drugs may be placed in the clean room, to allow for containment of the drug in case of a spill. 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.

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.

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[72] Public Health Agency of Canada (PHAC). *National vaccine storage and handling guidelines for immunization providers*. Ottawa, ON: PHAC; 2007. p. 22. Available from: http://www.phac-aspc.gc.ca/publicat/2007/nvshglp-ldemv/pdf/nvshglp-ldemv-eng.pdf

[73] 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

[74] *Drug and Pharmacies Regulation Act*, R.S.O. 1990, c. H.4. Available from: http://www.e-laws.gov.on.ca/html/statutes/english/elaws_statutes_90h04_e.htm

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.

**Cameras 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 use and installation 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 must be resistant to damage from cleaning/disinfecting and decontamination products. Personal electronic devices or accessories (cellphone, iPods, earbuds) are not permitted in either the ante 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 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 (PPE)[75]

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)
- the outer glove must be sterile

Non-sterile gloves that meet the ASTM International standard can be used in unpacking areas, the "dirty" area of the anteroom, storage areas and 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
- disposal of hazardous products

Glove changes

Both pairs of gloves must be discarded and replaced at the earliest of; manufacturer limit for permeation of the gloves, every 30 minutes[76] [77] [78], immediately if a tear, puncture or contamination has occurred or is suspected.

Hands and forearm hygiene must be performed each time gloves are changed.

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[75] 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. p. 4-5 to 4-11. Available from: http://www.asstsas.qc.ca/publications/publications-specialisees/guides-de-prevention/prevention-guide-safe-handling-of-hazardous-drugs.html

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

[77] 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.

[78] Association paritaire pour la santé et la sécurité du travail du secteur affaires sociales (ASSTSAS). *Prevention guide — safe handling of hazardous drugs.* Montréal, QC: ASSTSAS; 2008. pp. 4-5. Available from: http://www.asstsas.qc.ca/publications/publications-specialisees/guides-de-prevention/prevention-guide-safe-handling-of-hazardous-drugs.html

## Gown

The gown must be tested by the manufacturer to be resistant to permeability by hazardous drugs[79, 80]. The gown must close in the back (no open front). The gown must have long sleeves with fitted cuffs at the wrists.

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[81, 82] compounding work or after each removal or after a contamination has occurred or is suspected.

A gown is required if the employee is unpacking a damaged hazardous drug or if a spill has occurred[83].

## 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 contaminated[84].

## Mask

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

Surgical masks do not provide respiratory protection against drug exposure and therefore should not be used during compounding of hazardous preparations.

For most activities, an N95 or N100 mask (NIOSH approved) will protect against airborne particles.

No mask is necessary for unpacking hazardous drugs that have been received from the supplier in impervious plastic. However, if hazardous drugs have been

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[79] 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

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

[81] 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. p. 4-6. Available from: http://www.asstsas.qc.ca/publications/publications-specialisees/guides-de-prevention/prevention-guide-safe-handling-of-hazardous-drugs.html

[82] United States Pharmacopeial Convention (USP). General chapter <800>: hazardous drugs — handling in health care settings [draft]. Rockville, MD: USP; 2014 Mar.

[83] United States Pharmacopeial Convention (USP). General chapter <800>: hazardous drugs — handling in health care settings [draft]. Rockville, MD: USP; 2014 Mar.

[84] 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. p. 4.6. Available from: http://www.asstsas.qc.ca/publications/publications-specialisees/guides-de-prevention/prevention-guide-safe-handling-of-hazardous-drugs.html

damaged before receipt, a chemical cartridge respirator is required during unpacking[85].

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 BSC or for chemical decontamination after a spill can 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; 3.5 hours of continuous compounding work, after each removal or if contamination has occurred or is suspected.

**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<br><br>BSC with front window closed<br><br>Compounding in a CACI | N/A<br><br>N/A | Must be a mask specific for health care workers (not for construction workers)<br><br>Dust protection required |
| **Chemical-cartridge respirator** | Manipulation with splash risk | ISO Class 7 compounding room under negative | For organic vapour, gas and dust | Refer to manufacturer instructions to |

[85] United States Pharmacopeial Convention (USP). General chapter <800>: hazardous drugs — handling in health care settings [draft]. Rockville, MD: USP; 2014 Mar.

| | | | | |
|---|---|---|---|---|
| **with full face-piece or chemical cartridge respirator with face shield and goggles** | Cleaning a spill<br><br>Cleaning of C-PEC<br><br>Unpacking suspected damaged drugs from the supplier | pressure<br><br>BSC/CACI with front window open<br><br>Class 1 BSC for unpacking suspected damaged drugs<br><br>Anywhere a spill occurs | | determine frequency of filter change |

BSC = biological safety cabinet, CACI = compounding aseptic containment isolator, 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 face shield or a full face-piece respirator must be worn when working at or above eye level, cleaning the C-PEC, when cleaning a spill or there is risk of splashes to the face and eyes, unpacking suspected damaged drugs.

**Shoe covers**

Two pairs of disposable shoe covers are required at all times in the clean in the clean area of the ante room and the clean room Shoe covers are required even if dedicated shoes are worn. The shoe covers must be changed after each removal or in the event of contamination, spill or breakage[86]. Shoe covers prevent the contamination of shoes and subsequent spread of contamination to other areas of the facility[87]. Shoe covers 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.

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

**Uniform**

Compounding personnel shall wear clean room scrubs instead of street clothes. Use of clean room scrubs reduces the risk of contaminating the environment

[86] 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. p. 4.6. Available from: http://www.asstsas.qc.ca/publications/publications-specialisees/guides-de-prevention/prevention-guide-safe-handling-of-hazardous-drugs.html

[87] 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. p. 4.8. Available from: http://www.asstsas.qc.ca/publications/publications-specialisees/guides-de-prevention/prevention-guide-safe-handling-of-hazardous-drugs.html

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 preparations[88].

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

Only trained and qualified cleaning and disinfecting personnel must be allowed to clean controlled areas[89].

**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 could be used for decontamination. Example: 70% isopropyl alcohol, sterile water, peroxide, sodium hypochlorite. (*See* sections 5.3.4.5 and 6.6.4.3 for frequency of surface decontamination.)

Deactivation

Treatment of a hazardous drug to create a less hazardous agent. One method is chemical deactivation. The safety data sheets for some hazardous drugs recommend sodium hypochlorite. For chemical deactivation, sodium hypochlorite is usually a 2% solution. Sodium hypochlorite will corrode stainless steel surfaces, therefore sodium hypochlorite is removed/neutralized with sodium thiosulfate or with a germicidal detergent. Surface Safe™ (Hospira) is a

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

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

commercially available system of wipes containing both of these substances[90]. Sodium hypochlorite also has an additional germicidal effect for disinfection[91].

Disinfection
Destroying microorganisms. Disinfection must always be preceded by decontamination of the surface (*see* sections 5.3.4.5 and 6.6.4.3).

### 5.3.4.2 Disinfectant

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

The sterile compounding supervisor must

- initially choose 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 agent[92].

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

### 5.3.4.3 Equipment used for cleaning and disinfection and its storage

To avoid cross-contamination and to protect cleaning and disinfecting personnel, cleaning equipment must be designated for cleaning areas used for the compounding of hazardous sterile preparations[93, 94].

Non-shedding[95] equipment must be used for cleaning controlled areas. This equipment (mop, towels, etc.) should be disposable.

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[90] 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. p. 13-2. Available from: http://www.asstsas.qc.ca/publications/publications-specialisees/guides-de-prevention/prevention-guide-safe-handling-of-hazardous-drugs.html

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

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

[93] 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.

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

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

#### 5.3.4.4 Garbing of cleaning and disinfecting personnel

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 glove must be sterile. .

#### 5.3.4.5 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 monthly.[96]

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

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

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

- walls
- ceiling
- shelves
- area outside the containment primary engineering control (this must be decontaminated along with cleaning and disinfecting)

Cleaning should be done from the "cleanest" area to the "dirtiest" area: i.e. the end of the clean room toward the anteroom exit.

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

## 5.4 General maintenance log

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

[96] 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.

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

- cleaning and disinfecting, facility certification and maintenance, C-PECs certification and maintenance and other equipment maintenance;
- 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.

# 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 start before the BUD has been exceeded[97].

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 preparation's risk of contamination.

Where no specific sterility test is performed for a preparation or batch, the sterile compounding supervisor must assign a BUD based on the following criteria:

***The BUD must not exceed the <u>earliest</u> of the dates established by the following two criteria:***

- expiration date based on chemical and physical stability[98,99,100] according to reference texts;
- storage time related to risk of microbial contamination[101]

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

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

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

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

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

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

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

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

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

The BUDs for commercial products used for compounding of hazardous sterile preparations specified in the following three sections (6.1.2.1, 6.1.2.2 and 6.1.2.3) apply when the products are stored in the original package and container.

#### 6.1.2.1 Single-dose vial

- a single-dose is labelled as such from the manufacturer. Single dose vials include pharmacy "bulk" vials if they are labelled as single dose from the manufacturer.
- The vial is punctured in a C-PEC that maintains ISO Class 5 air quality, the BUD is 6 hours[102] .
- Six hours after initial needle puncture, the vial cannot 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 single dose container is opened or punctured in worse than ISO Class 5 air quality, the BUD is 1 hour.

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

#### 6.1.2.2 Open ampoule

- BUD: no storage permitted

#### 6.1.2.3 Multiple-dose container (ex. Vials)

- Labelled as such from the manufacturer
- Usually contains a preservative
- BUD: 28 days, unless otherwise specified by the manufacturer.
- If there is visible contamination prior to 28 days (or manufacturer expiry date), the container is to be discarded

### 6.1.3 Beyond-use date according to risk of microbial contamination

Compounded medications are at risk of microbial contamination. Time and temperature can allow for 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 onset of contamination.

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) are for 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

**<u>Sterile unit</u>**

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

**Table 6**

| Contamination risk levels[103,104] | | |
|---|---|---|
| **Low** | **Medium** | **High** |
| • Final product compounded using up to 3 “sterile units”<br>• No more than 2 septum punctures at the injection site for each sterile unit<br>• Simple aseptic transfer technique<br>• Drug prepared for one patient (patient-specific dose) | • Final product compounded using 4 or more “sterile units”<br>• Complex manipulations<br>• Prolonged preparation time<br>• Batch preparations (preparing for more than one unit of the same composition during one compounding session) | • Non-sterile ingredients or equipment used before terminal sterilization<br>• Non-sterile water-containing preparations stored for more than 6 hours before terminal sterilization<br>• Compounding personnel are improperly garbed and gloved. |

**Table 7**

| Beyond-use dates (BUDs) for hazardous compounded sterile preparations, according to risk of microbial contamination[105] | | | |
|---|---|---|---|
| | **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 |

[103] United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013.
[104] 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. Available from: http://www.ashp.org/s_ashp/docs/files/discguide797-2008.pdf
[105] United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013. pp. 365-7.

Administration of the compounded sterile preparation must start before the BUD has been exceeded.

High-risk preparations must always be sterilized (the BUDs in Table 7 apply to high-risk *sterile* preparations).

**Bacterial Endotoxin test**[106]

A bacterial endotoxin test must be performed for high-risk hazardous compounded 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 preparations

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

#### 6.1.4.1 Beyond-use dates for immediate-use preparations

Hazardous sterile preparations do not qualify as immediate-use preparations (as defined in USP 797)

#### 6.1.4.2 Beyond-use dates of 12 hours or less for preparations compounded in segregated areas [107]

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

- The C-PEC is certified every 6 months and maintains an 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.
- Preparations are low or medium risk.

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

[107] United States Pharmacopeial Convention (USP). General chapter <800>: hazardous drugs — handling in health care settings [draft]. Rockville, MD: USP; 2014 Mar.

- 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.
- Sink is not adjacent to the C-PEC. Sink separated from the immediate area of the C-PEC.
- No unsealed windows and no doors 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.
- Full compliance with hand and forearm hygiene, asepsis, garbing and cleaning and disinfecting

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

## 6.2 Compounded sterile preparation protocols

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

- name of preparation
- pharmaceutical form
- all required ingredients
- quantity concentration and source of ingredients
- necessary equipment
- procedure for compounding the preparation
- storage method
- 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 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 individual patients, 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 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 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 when 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 provincial/territorial authorities.

### 6.3.2 Hazardous compounded sterile log for preparations made in batches

The log for hazardous 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
  - equipment needed to prepare the preparation, when appropriate
  - mixing instructions should include: order of mixing, mixing temperatures or other environmental controls, duration of mixing and, other factors pertinent to the replication of the preparation as compounded
- for each ingredient (including primary and secondary diluents),
  - name
  - quantity/volume measured
  - calculation 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 when applicable
  - expiration date
- quantity prepared
- 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, prescription or control number (batch number), whichever is applicable
- compounding date
- container used in dispensing
- packaging and storage requirements
- description of the final preparation
- quality control procedures and expected results
- identity of compounder and verifier at each stage of the process as well as identity of the person who approved the preparation

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

## 6.4 Patient file

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

Information recorded in the patient's 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's file in situation where the preparation was made by another pharmacy, as permitted by provincial/territorial legislation).

Any pharmacies (health care facility or community) must be able to track information related to preparations even of the 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 policies and procedures.

No matter which C-PEC is used for sterile compounding, all of section 6.5 applies

### 6.5.1 Conditions that may affect preparation quality

Any of the following conditions affect preparation quality[108]. Personnel afflicted with any of the following conditions shall be excluded from sterile compounding activities and sterile compounding areas until their conditions are remedied:

- uncontrolled weeping skin condition;
- burns to the skin, including sunburns;
- cold sores (active herpes simplex viral infection);
- conjunctivitis (viral or bacterial);

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

- active respiratory infection with coughing, sneezing or runny nose;
- fresh piercings;
- other fresh wounds.

A person with permanent tattoos may compound sterile preparations. 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 must[109]:

- remove personal outer garments (e.g., coat, hat, jacket, scarf, sweater, vest, boots and outdoor shoes);
- remove jewellery, studs and other accessories from fingers, wrists, forearms, face, tongue, ears and neck. This includes removal of personal electronic devices or accessories (cell phone, Ipods, earbuds, etc.) which are not permitted in the ante or clean room;
- remove all cosmetics (makeup, false eyelashes, henna tattoos, paper tattoos, perfume and hair products such as hairspray), which can produce particles that are possible sources of contamination;
- tie up long hair;
- remove nail polish[110] and other nail applications. Nail extensions or other synthetic nail-lengthening products are prohibited;
- ensure that natural nails are kept short and trimmed (1/4 " CDC);
- 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)

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

[110] Boyce JM, Pittet D. 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):1-45.

In controlled areas, the following measures should be taken:

- Food items, drinks, chewing gum, candy and smoking are prohibited[111].
- 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 area.
- 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.
- All personnel in the controlled area must follow hand hygiene and garbing procedures.

## 6.6 Aseptic compounding of hazardous sterile preparations[112,113]

### 6.6.1 General

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

- performing hand and forearm hygiene;
- garbing of personnel;
- disinfecting and introducing products and equipment into the clean room;
- disinfecting the 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, 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 activities[114].

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

[112] Association paritaire pour la santé et la sécurité du travail du secteur affaires sociales (ASSTSAS). Chater 8 : [Drug Preparation. *Prevention guide — safe handling of hazardous drugs.* Montréal, QC: ASSTSAS; 2008. pp. xx-yy. Available from: http://www.asstsas.qc.ca/publications/publications-specialisees/guides-de-prevention/prevention-guide-safe-handling-of-hazardous-drugs.html

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

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

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 in 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.. Hand hygiene is required, regardless of the type of C-PEC used for sterile compounding.

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 then 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 to the elbows with soap and water, for a period of not less than 30 seconds. Do not use brushes.
- Rinse with water.
- Dry hands and forearms with disposable, lint-free towel.
- Dispense alcohol-based hand rub with persistent activity (ABHR) onto one palm.
- Immerse fingertips of the other hand into the ABHR.
- Cover the forearm of the other hand with ABHR until the ABHR evaporates.
- Repeat with other hand and other forearm.
- Don gown.
- Enter the clean room.
- Dispense ABHR onto palm of one hand. Rub both hands with ABHR, making sure that all surfaces of the hands are covered. Continue to rub until the ABHR has evaporated.
- Allow hands to dry.
- Don gloves. For hazardous drug compounding, don two pairs of gloves. The outer glove must be sterile.

The hand washing sequence must be documented in the policies and procedures and updated as appropriate[115].

#### 6.6.2.2 Garbing

Personnel must wear the PPE required for compounding hazardous sterile preparations. PPE is required, regardless of the type of containment primary engineering control[116].

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 general garbing sequence is as follows:

- Don hair net, then don beard cover (if required) and then don face mask on the dirty side of the demarcation line;
- Don two pairs of shoe covers while stepping over the demarcation line
- Hand hygiene as per hand and forearm hygiene 6.6.2.1;
- Don gown;
- Apply alcohol based hand scrub with persistent activity to hands and allow hands to dry;
- Don gloves

Any compounder 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. For compounding personnel, the outer glove must be sterile.

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

After finishing the compounding of hazardous sterile preparations, personnel must remove their 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 and performing any other activity.

### 6.6.3 Introducing products and equipment into the clean room

Before a product enters the anteroom, it must be removed from cardboard shipping boxes. The product must be wiped with a sporicidal agent (since cardboard has been found to harbour mould spores). Any remaining packaging

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

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

must be removed after the product enters 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 CACI[117]. Disinfect equipment and products by wiping them with sterile 70% isopropyl alcohol. Do not spray components. 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. 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 then introduced into the clean room. The equipment and products are disinfected while being transferred onto the clean cart or bin.

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

Only compounding personnel are allowed to decontaminate, deactivate and disinfect the C-PEC. They must take the following steps:

- Follow hand and forearm hygiene and garbing procedures.
- Follow the decontamination, deactivation and disinfection methods described in the pharmacy's procedures (respecting specified equipment, sequence, movements, frequency, etc.).

Only the person performing this maintenance should be present in the clean room[118].

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 swabs.

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

[118] 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.

- Avoid contaminating the surface of swabs used for cleaning and disinfecting.
- Change swabs after completing disinfection of each section of the C-PEC.
- Disinfect the BSC or CACI with sterile 70% isopropyl alcohol or another disinfecting agent, using sterile swabs, at the start and end of the day or shift (minimum twice per day).
- Follow the disinfecting method described in the pharmacy's procedures.
- Wait until the disinfectant has dried before compounding the first preparation in the C-PEC[119].
- Record cleaning and disinfecting activities in the maintenance log.

If the disinfectant is a concentrated product and needs to be diluted, the use of sterile water shall be used for diluting disinfectant solutions used inside the ISO Class 5 device. Always dilute the disinfectant according to manufacturer instructions.

#### 6.6.4.2 Decontamination of the C-PEC

On its own, sterile 70% isopropyl alcohol does not decontaminate hazardous drugs and may, on the contrary, spread any chemical contamination that is present to other surfaces.[120,121,122]. Therefore, for daily activities such as disinfecting the inside of the BSC, a surface decontamination step using a germicidal disinfectant detergent[123], must precede the usual disinfection step performed with sterile 70% isopropyl alcohol.

#### 6.6.4.3 Frequency of surface decontamination, deactivation and disinfection for C-PECs

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 and disinfection are performed at a different frequency, it should be established and justified on the basis of environmental control results.

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

[120] 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.

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

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

[123] Association paritaire pour la santé et la sécurité du travail du secteur affaires sociales (ASSTSAS). Chapter 7: Planning the Oncology Pharmacy. *Prevention guide — safe handling of hazardous drugs.* Montréal, QC: ASSTSAS; 2008. pp. 7-3. Available from: http://www.asstsas.qc.ca/publications/publications-specialisees/guides-de-prevention/prevention-guide-safe-handling-of-hazardous-drugs.html

The material safety data sheets for a few hazardous products indicate that they are deactivated by sodium hypochlorite. Sodium hypochlorite will corrode stainless steel. Therefore, sodium hypochlorite is followed by sodium thiosulfate for neutralization or sodium hypochlorite is removed with a germicidal detergent. The deactivation frequency recommended for C-PECs is indicated in Table 8.

**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**[124,125,126,127,128] | **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<br>- At the start or end of each shift<br>- Where surface contamination is suspected<br>- If there has been non-compliance with aseptic techniques | ✓ | | ✓ |
| All surfaces inside BSC or CACI | - At start of workday<br>- At start of workday if BSC or CACI has not been used for one or more days<br>- When there has been a spill | ✓ | | ✓ |
| 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 = germicidal disinfectant detergent, followed by rinsing with water.<br>†Deactivation = application of sodium hypochlorite followed by sodium thiosulfate or germicidal detergent<br>‡Disinfection = application of sterile 70% isopropyl alcohol. | | | | |

[124] 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.

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

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

[127] 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

[128] Association paritaire pour la santé et la sécurité du travail du secteur affaires sociales (ASSTSAS). *Prevention guide — safe handling of hazardous drugs.* Montréal, QC: ASSTSAS; 2008. pp. 13–2 and 13–3. Available from: http://www.asstsas.qc.ca/publications/publications-specialisees/guides-de-prevention/prevention-guide-safe-handling-of-hazardous-drugs.html

### 6.6.5 Aseptic techniques for compounding hazardous sterile preparations

#### 6.6.5.1 General

Compounding personnel must use first-air and use meticulous aseptic technique when preparing compounded sterile preparations. One preparation must be completed from the start to finish before compounding begins on the next preparation.

In the event of non-compliance with aseptic technique, the preparation must be discarded. In this situation, new supplies must be used. Decontaminate and disinfect the surface of the C-PEC before beginning another preparation.

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 surface[129]. For the frequency and circumstances of glove changes see section 5.3.3.3.

The external packaging of products and supplies must be intact, dry and unsoiled. Otherwise, the products and supplies must be discarded. 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 while equipment is being disinfected.

Vials must not be allowed to accumulate in the C-PEC in order to reduce the risk of errors and to decrease turbulent air flow from the C-PEC.

#### 6.6.5.2 Aspects of compounding hazardous preparations

**<u>Interior of C-PEC</u>**

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

- use a ventilated system equipped with a 0.22-µm hydrophobic filter when diluting powder or withdrawing liquids;
- when withdrawing a hazardous preparation 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;

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

- if possible, use a closed-transfer system (since the steps described above do not completely eliminate 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 procedure [130] on all surfaces of the container.

While the final container is still inside the C-PEC[131], compounding personnel must label it and place it in a sealable plastic bag[132]. 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 (or compounding pharmacist or pharmacy technician) must perform the following activities:

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

When compounding, 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

[130] 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. p. 8-7. Available from: http://www.asstsas.qc.ca/publications/publications-specialisees/guides-de-prevention/prevention-guide-safe-handling-of-hazardous-drugs.html

[131] 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. p. 8-7. Available from: http://www.asstsas.qc.ca/publications/publications-specialisees/guides-de-prevention/prevention-guide-safe-handling-of-hazardous-drugs.html

[132] 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. p. 8-7. Available from: http://www.asstsas.qc.ca/publications/publications-specialisees/guides-de-prevention/prevention-guide-safe-handling-of-hazardous-drugs.html

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).

To note that if the verifier is going into the clean room, the person must be garbed exactly as the compounding personnel. If verification occurs in the anteroom (i.e. via camera/image capture) then the person would need a hair cover, gown, two pairs of ASTM tested gloves, shoe covers.

#### 6.6.6.2 Process for verification

Verifications 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 compounded 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.

#### 6.6.6.5 Second verification

Each preparation must be inspected by a person other than the individual who performed the aseptic technique. 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 integrity.[133]

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

### 6.6.7 Labelling 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

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

the requirements of the applicable legislation and regulation.

All active ingredients must be identified on the label. The label must also include the amount 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 for a patient 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 it occurs;

- 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 and poisons 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 is undertaken by another pharmacy, as permitted by provincial/territorial legislation), provided there is demonstrable agreement between the two pharmacies.

## 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 maintain the preparation’s stability and integrity as well as storage conditions for stability.

### 6.7.1 Packaging process

During packaging, compounding personnel must

- put all final hazardous compounded sterile preparations in a clear plastic bag (or an amber bag, if the preparation must be protected from light);
- 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 transportation 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 (packaging must maintain a temperature between 2°C and 8°C for hazardous compounded sterile preparations requiring refrigeration and a temperature between 19°C and 25°C for hazardous compounded sterile preparations to be kept at room temperature);
- method to be used to confirm whether the temperature of hazardous compounded sterile preparations has been maintained during transport (use of temperature maintenance indicator, min/max thermometer, certified cooler, etc.);
- 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 stability at these temperatures.

## 6.8 Receipt and storage of hazardous products[134]

A sample procedure for receiving, unpacking and storing hazardous products is provided 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.

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

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

1. Seal the container and return to supplier in an impervious container. Label the container as hazardous. Contact supplier for instructions
2. Unpack the shipping container in a Class I containment device used for non-sterile hazardous drug compounding. Place a plastic backed prep mat on the work surface of the Class I device. Open package and remove usable items. Wipe the outside of items with a disposable wipe. Enclose the damaged item(s) in an impervious container. Label the container as hazardous. Contact the supplier for instructions.
   (*see also* section 6.11.2).

#### 6.8.1.1 Containers and packaging of goods received

A container, box or outside bag containing an order 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 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 are to 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 waste container.

#### 6.8.1.2 Garbing of personnel for unpacking

For unpacking intact hazardous products, received from the supplier sealed in impervious plastic, the following garb is required[135]:

- two pairs of ASTM International–approved gloves

For unpacking suspected damaged hazardous products, the following garb is required[136]:

- 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 respirator
- chemical cartridge respirator

[135] United States Pharmacopeial Convention (USP). General chapter <800>: hazardous drugs — handling in health care settings [draft]. Rockville, MD: USP; 2014 Mar.

[136] United States Pharmacopeial Convention (USP). General chapter <800>: hazardous drugs — handling in health care settings [draft]. Rockville, MD: USP; 2014 Mar.

Damaged hazardous drugs must be unpacked in a Class I containment device used for non-sterile hazardous drugs.

### 6.8.2 Storage of hazardous products

#### 6.8.2.1 Storage criteria

The sterile compounding supervisor must develop a storage procedure (*see* Appendix 5), and it 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)[137] 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 preparations, the storage temperature must be controlled and must remain within the limits specified in Appendix 11, Information on temperature in the storage area for hazardous products and the refrigerator or freezer, must be kept in the maintenance log[138].

During storage, the temperature must be maintained with the range specified by the BUDs of final preparations and products, regardless of the season. Alternative storage must be provided if the storage temperature exceeds acceptable variations and during cleaning of refrigerators and freezers.

#### 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 final hazardous compounded sterile preparations

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

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

Policies and procedures must be developed and implemented for the transport of hazardous compounded sterile preparations and their delivery to patient care units, patients and dispensing pharmacists (*see* Appendix 5). 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 (pharmacists, pharmacy technicians, pharmacy assistants and drivers) 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 they have been properly stored (at the correct temperature, with protection from light, etc.) and there is no evidence of tampering[139].

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 ensure that transport conditions are maintained until delivery to the patient.

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

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[139] 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

In community or hospital pharmacies, when information obtained as a result of an 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/pharmacy technician must be able to

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

The information on 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.

In health care facilities, the pharmacist/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 that led to the recall must be reviewed, and corrective and preventive measures must be identified and implemented, regardless of the location of the pharmacist's practice.

## 6.11 Incident and accident management

### 6.11.1 Accidental exposure[140]

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

[140] 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. p. 12-5. Available from: http://www.asstsas.qc.ca/publications/publications-specialisees/guides-de-prevention/prevention-guide-safe-handling-of-hazardous-drugs.html

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 soap[141]. A physician should be consulted.

The exposure must be documented in the appropriate logs.

### 6.11.2 Spills

Policies and procedures

Policies and procedures for managing spills must be established (*see* Appendix 2).

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). In health care facilities or community pharmacies, a form developed or selected by the facility/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

[141] 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. p. 12-5. Available from: http://www.asstsas.qc.ca/publications/publications-specialisees/guides-de-prevention/prevention-guide-safe-handling-of-hazardous-drugs.html

recurrence. Each organization needs to have a process for this activity and maintain a log. Information is used to investigate deviations and improve processes.

## 6.12 Hazardous waste management

In the performance of assigned duties, the pharmacist/pharmacy technician must[142]

- ensure that medications and sharp or pointed instruments are disposed of safely in compliance with the 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 products.[143] A list of hazardous products in use must be available in the pharmacy. The list produced by NIOSH, which is part of the US Centers for Disease Control and Prevention[144] can be used to determine if a particular product is hazardous.

Policies and procedures for the management of hazardous waste[145] must be developed and followed. These policies and procedures must comply with local, provincial and federal requirements.

The policies and procedures must include the following provisions:

- All personnel involved in the management of hazardous product waste must receive appropriate training on destruction procedures to ensure their own protection and to prevent contamination of the premises or the environment[146].
- 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"[147]. Containers should be filled to only three-

[142] 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

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

[144] 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

[145] 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. p. 12-2. Available from: http://www.asstsas.qc.ca/publications/publications-specialisees/guides-de-prevention/prevention-guide-safe-handling-of-hazardous-drugs.html

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

quarters of their capacity[148]. 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 into the hazardous waste container.
- Bins used for hazardous product waste must comply with local, provincial and federal requirements. These bins must be incinerated and may not be sent for decontamination by autoclave and subsequent burial.

# 7. QUALITY ASSURANCE PROGRAM

A quality assurance program must be established by the sterile compounding supervisor to ensure the clear definition, application and verification of all activities that will affect the quality of the hazardous compounded sterile preparations and the protection of personnel.

The quality assurance program is established to give personnel and other responsible individuals information showing that the personnel, facilities and equipment (C-PEC, etc.) attain and maintain the conditions required for contamination-free compounding of hazardous sterile preparations and also that the hazardous sterile preparations are being compounded in compliance with established procedures.

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

## 7.1 Program content

[147] 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. p. 12-2. Available from: http://www.asstsas.qc.ca/publications/publications-specialisees/guides-de-prevention/prevention-guide-safe-handling-of-hazardous-drugs.html

[148] 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. p. 12-3. Available from: http://www.asstsas.qc.ca/publications/publications-specialisees/guides-de-prevention/prevention-guide-safe-handling-of-hazardous-drugs.html

The sterile compounding supervisor must establish a quality assurance program that has 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 sterile compounding supervisor must record and retain proof of calibration of the thermometer.

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

A computerized temperature monitoring may be acceptable when the system provides features to record and store temperature readings at a minimum at the same frequency. The system also needs to trigger an alarm if the temperature readings deviate from the acceptable range.

### 7.3.2. Verification of controlled rooms and containment primary engineering control (C-PEC)

#### 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 months[149];
- 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

[149] 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

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 reception, storage, preparation and verification of products and preparations, in addition to verifying the microbiological contamination of controlled areas twice per year.

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

The sterile compounding supervisor must ensure that 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 controlled 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, should it be necessary. A procedure must be developed to outline and explain the actions to be taken should the pressure differential be non-compliant.

The indicators verified for proper operation of any device (BSC, CACI, ACD, etc.) shall be verified every day, and data should be recorded in the general maintenance log.

**Sampling of non-viable, viable and surface particles in controlled areas and the C-PEC**[150] [151]

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 CAG-002, CETA CAG-003 and CETA 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

[150] United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. In: *USP pharmacists' pharmacopeia* . 2nd ed., Suppl. 2. Rockville, MD: USP; 2008. Section "Sampling plan," p. 12.

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

- sampling methods to be used
- number of samples to be obtained at each site
- frequency of sampling
- number of CFUs triggering action

The sampling plan must allow for three types of samples:

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

Sampling specifications

Samples must be obtained at least every 6 months from the air in controlled areas and in the C-PEC[152] *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 the 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 months[153] 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 the 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.

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

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

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 the certification activities and the standards used by the 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 liters for ISO Class 5, 500 liters for all other areas);
- surface sampling of each established sampling site, using a 55 mm agar surface. Gently touch the sample site with the agar surface. Use a new agar plate for each sampling site.. The agar will leave a residue behind. Immediately after sampling with an agar plate disinfect the sampled area.

The sampling of viable air and surface particles must be performed by a qualified individual such as a certifier or by 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.

The sterile compounding supervisor must:

- obtain from the manufacturer a calibration certificate for the viable air sampler, to ensure that it is regularly calibrated according to the manufacturer's recommendations and to properly train 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 of other media that supports the growth of fungi
- assure the microbial proliferation capacity of each batch of nutrient medium used (the certificate for this test, provided by the manufacturer, must be retained[154]).

The samples obtained must be either:

- sent to a certified external laboratory; or
- incubated in the community or health care facility pharmacy, provided that

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

- 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 incubated[155]. Tryptic soy agar (TSA) should be incubated between 30°C and 35°C for 48 to 72 hours. Malt extract agar other fungal media should be incubated between 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 classification[156]. The following contamination levels will require corrective action:.

Volumetric sampling of facility air:

- Areas requiring ISO Class 5 air quality, threshold contamination > 1 CFU/$m^3$ of air
- Areas requiring ISO Class 7 air quality, threshold contamination > 10 CFU/$m^3$ of air
- Areas requiring ISO Class 8 air quality, threshold contamination > 100 CFU/$m^3$ 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 a growth of any viable particles via air sampling, surface sampling or GFS, the genus of the microorganism must be identified. The sterile compounding supervisor will then establish corrective and preventive actions based on this information. The sterile compounding supervisor must analyze the data obtained and the trends observed with respect to the microbial. If necessary, the sterile compounding supervisor should consult a microbiologist or infectious disease specialist.

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

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

**Hazardous drug contamination/Wipe sampling**

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

The level of hazardous drug contamination should be measured at least once a year, more frequently if a 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 put in place (as described in the ASSTSAS guide[157]), 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 maintenance log.

## 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 Sampling (GFS)[158]

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, 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 polysorbate[159], the assessor takes thumbprints and prints of each gloved fingertip from both hands of the

[157] 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: http://www.asstsas.qc.ca/publications/publications-specialisees/guides-de-prevention/prevention-guide-safe-handling-of-hazardous-drugs.html

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

[159] 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.

assessed employee, asking the employee to gently press 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. Hand and forearm hygiene is then performed.

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

The first GFS (obtained after sterile gloves are put on) must be successfully completed three times before the personnel is permitted to compound sterile preparations. Successful completion is zero CFU.

The GFS obtained after the media fill test must be completed annually for low and medium risk compounding and every 6 months for high risk sterile compounding. Total CFUs for both hands must be less than or equal to 3 CFUs. More than 3 CFUs will prompt the sterile compounding supervisor to investigate work practices, procedures, 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 to verify maintenance of the aseptic process for a given employee. For more information on this test, consult General Chapter <797> in the USP–NF[160].

For the media fill test, the simulation chosen for assessment of personnel 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 there[161].

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 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 the nutrient medium used must have been tested by the manufacturer, and the certificate for this test result must be retained by the compounding pharmacy[162].

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 that procedures are in place for its use and maintenance

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

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

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

and for the surveillance of required temperatures. Personnel must be properly trained to read the results.

The containers filled with the nutrient medium to be used for the media fill test must be incubated between 20°C and 25°C or between 30°C and 35°C for 14 consecutive days[163]. 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 sterile preparation;
- compliance of the preparation with the prescription issued;
- compliance (with legislation and regulations) of labels affixed to containers;
- compliance with required documentation in a patient's hazardous compounded sterile preparations log 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.

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

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

All completed documentation concerning components of the environmental verification of controlled areas, the C-PEC and support equipment must be filed and retained with other compounding records in an easily accessible location inside the pharmacy.

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

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

## 8.0 SOURCE FOR ADDITIONAL INFORMATION

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

For more information on hazardous compounding, please refer to chapter <800> in future editions of USP-NF. At the time of the publication of the Model Standards chapter <800> was in draft form.

# 8. GLOSSARY

| Term | Definition |
|---|---|
| Accident | 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, professional concerned or third party. An accident differs from an incident, which has no effect on the patient. |
| Anteroom | A room equipped with two doors, with system/procedures that allows only one door to open at a time, which allows passage or movement of someone or something from one environment to another, while keeping these environments isolated from each other. |
| Aseptic techniques | Steps in the aseptic process that include all manipulations performed inside the primary engineering control by compounding personnel. |
| Assessment | Action of assessing and defining an employee's performance and competency. |
| Beyond-use date (BUD) | For the purposes of these Model Standards, administration of the compounded sterile preparation must start before the BUD has been exceeded[164]. |
| Biological safety cabinet (BSC) | Laminar airflow workbench that is ventilated to protect personnel, hazardous sterile compounded preparations and the immediate environment. The open front of a BSC has the following features:<br>• air intake, to protect compounding personnel from hazardous sterile preparations;<br>• descending air curtain filtered with a high-efficiency particulate air filter to protect the hazardous sterile product;<br>• air evacuation system equipped with high-efficiency particulate air filters for environmental protection[165]. |
| Cleaning | Removal of dirt, dust and other substances that may host microorganisms,[166]. |
| 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 a specific level. The room is designed to minimize introduction, generation and retention of particles. In this case, an ISO Class 7 environment. |
| 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 |

[164] United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013.
[165] 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/prevention/reptox/whmis/material-safety-data-sheet-users-guide/pages/table-contents.aspx
[166] United States Pharmacopeial Convention (USP). General chapter <1072>: disinfectants and antisepsis. In: *USP pharmacists' pharmacopeia.* Rockville, MD: USP; 2008–2009.

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| | required for competent performance of duties by members of a profession, |
| Compounding | Act of preparing something, through preliminary work, to put it into a usable state. Also refers to the material that has been compounded (e.g., a chemical or pharmaceutical preparation). |
| Compounding aseptic containment isolator (CACI) | Isolator specifically used for compounding hazardous sterile preparations. 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.<br><br>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. |
| Compounding personnel | Pharmacists, pharmacy technicians 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 oducts 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 compounding is undertaken by another pharmacy, as permitted by provincial/territorial legislation). |
| Compounding procedure | Procedure that describes all the 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 and with which the compounder must comply. The protocol must include all of the information to be recorded in the preparation log. |
| Containment Primary Engineering Control | A device that provides an ISO Class 5 environment for the exposure of critical sites during aseptic compounding and designed to minimize airborne contamination of hazardous products in order to protect workers and the environment from hazardous drug exposure.<br><br>For hazardous drug compounding, containment primary engineering controls include biological safety cabinets (BSCs) and compounding aseptic containment isolators (CACIs). |
| Containment system | Arrangement or equipment to contain the particles of hazardous products in the chosen space. |
| Contiguous | A term describing a location or space that adjoins another.<br><br>Example: The clean room is contiguous with the anteroom and the surrounding pharmacy areas.<br><br>Synonyms: adjacent, adjoining, bordering, abutting, surrounding, neighbouring |

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| 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 obtain the specified ISO class parameters, the concentration of viable and non-viable particles suspended in the air is verified according to a sampling plan. Corrective measures are taken when necessary so that the area remains at the expected ISO class level.[167] The clean room and anteroom are examples of controlled areas. May also be 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 or air filtered by means of a high-efficiency particulate air filter or humidity (oral secretions or mucous membranes) or likely to be contaminated by touch[168]. |
| Deactivation | Treatment of a hazardous drug to create a less hazardous agent . One method is chemical deactivation[169]. |
| Decontamination | Transfer of a hazardous drug contaminant from a fixed surface (ex. counter, bag of solution) to a disposable surface (ex. wipe, cloth). The wipe is then contained and discarded as hazardous waste[170]. |
| 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[171]. |
| Disinfection | Treatment that eliminates most of the pathogens present on an object or surface[172]. |
| Facilities | All devices, rooms and spaces that are organized, arranged and modified to better adapt them to the activities to be conducted therein.<br>Facilities include the clean room and the anteroom. |

[167] United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013.
[168] United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013.
[169] 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: http://www.asstsas.qc.ca/publications/publications-specialisees/guides-de-prevention/prevention-guide-safe-handling-of-hazardous-drugs.html
[170] 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: http://www.asstsas.qc.ca/publications/publications-specialisees/guides-de-prevention/prevention-guide-safe-handling-of-hazardous-drugs.html
[171] United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013.
[172] United States Pharmacopeial Convention (USP). General chapter <1072>: disinfectants and antisepsis. In: *USP pharmacists' pharmacopeia.* Rockville, MD: USP; 2008–2009.

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| Dispensing a prescription | All activities relating to the validation (including therapeutic appropriateness), preparation and packaging of a patient's medication prepared pursuant to a prescription. |
| Final sterile preparation | A sterile preparation ready to be stored and then administered to a patient, which has been prepared according to a preparation-specific compounding protocol which respects the prescribing physician's prescription. |
| Gloved fingertip sampling (GFS) | Using tryptic soy or agar contact plate with lecithin and polysorbate, the assessor takes thumbprints and prints of each gloved fingertip from both hands of the assessed employee. The employee gently presses each thumb and fingertip on the agar in the contact plate. One agar plate for each hand.[173] The agar is then incubated and the CFU counted. |
| Hand hygiene | All methods related to hand washing that is performed using 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 toxicity or damage organs[174].<br>Drugs are considered hazardous because they involve risks for the worker, because of their effects[175]. |
| Hazardous material | A material that, because of its properties, constitutes a danger to an employee's health, safety or physical integrity[176]. 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*[177]. |
| Hazardous products | Substances that entail risks for the worker because of their effects. For the purposes of these Model Standards, the term "hazardous product" refers to both hazardous drugs and hazardous materials, depending on the situation. |
| Incident | An action or situation that has no impact on the health status or well-being of the user (patient), personnel, professional concerned or third party, but which as an unusual result that could, on other occasions, lead to |

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

[174] 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

[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: http://www.asstsas.qc.ca/publications/publications-specialisees/guides-de-prevention/prevention-guide-safe-handling-of-hazardous-drugs.html

[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: http://www.asstsas.qc.ca/publications/publications-specialisees/guides-de-prevention/prevention-guide-safe-handling-of-hazardous-drugs.html

[177] *Controlled Products Regulations,* SOR/88-66, 1987. Available from: http://laws-lois.justice.gc.ca/eng/regulations/SOR-88-66/

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| | consequences. An incident differs from an accident, which has or could have an impact on the patient[178]. |
| Incubator | A device used 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 the drugs prepared or sold with or without a prescription. It is usually computer-generated and adhesive. It must bear the information 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.<br>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[179]. |
| 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. The employer should have it before a product is used for the first time"[180]. |
| Media fill test | Test used to qualify aseptic techniques of compounding personnel and the environment's ability to produce preparations that are "sterile." For this test, a nutrient medium replaces the actual product when the aseptic technique is performed[181,182]. |

[178] 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/prevention/reptox/whmis/material-safety-data-sheet-users-guide/pages/table-contents.aspx

[179] Canadian Nurses Association (CNA). *Joint position statement: Promoting continuing competence for registered nurses.* Ottawa, ON: CNA; 2004. Available from: http://www.cna-aiic.ca/~/media/cna/page-content/pdf-en/ps77_promoting_competence_e.pdf

[180] 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/prevention/reptox/whmis/material-safety-data-sheet-users-guide/pages/table-contents.aspx

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

[182] 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

| | |
|---|---|
| Multiple-dose container | Commercial drug container in multiple-dose format for parenteral administration only. The product usually contains an antimicrobial preservative[183]. |
| Personal protective equipment (PPE) | All garb and accessories, such as mask, gloves, gown and safety goggles, that protect the sterile preparation and the worker. It enables compliance with the expected specifications of a controlled environment and protects the worker from exposure to physical or chemical risks[184 185]. |
| Pharmacist | Registrant in good standing of one of the pharmacy regulatory authorities in Canada. |
| Pharmacy assistant | An adult who has earned a vocational school diploma for completing a pharmacy assistant course or any adult person who has received proper training that is deemed equivalent. |
| Pharmacy bulk vial | Commercial container for parenteral sterile preparations, intended for packaging containing 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 | An adult who has earned a college degree or diploma from an accredited pharmacy technician program and has passed the national examination. Such persons are 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 that presents the policy. |
| Prescription validation | The pharmacist's decision to declare a prescription valid after verifying its legality, contents and relevance with respect to the patient and the patient's condition. |
| Procedure | All steps to be taken, the means to be used and the methods to be followed in performing a task. |
| Process for aseptic compounding | All activities leading to completion of a final compounded sterile preparation, 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 compounded sterile preparations. Its purpose is to maintain the sterility of a preparation or drug compounded from sterile components. |

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

[184] 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: http://www.asstsas.qc.ca/publications/publications-specialisees/guides-de-prevention/prevention-guide-safe-handling-of-hazardous-drugs.html

[185] 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

| | |
|---|---|
| Protocol | Document describing in detail all steps to be followed or behaviours to adopt in precise 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.[186] Labelled as such from the manufacturer. |
| Stability (period of) | Length 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 department head of the health care facility or by the pharmacist owner of a community pharmacy to supervise and organize all activities related to the compounding of sterile preparations. |
| Sterilization by filtration | Using a sterilizing-grade membrane to produce a sterile final solution (where a sterilizing-grade membrane is a membrane approved for filtering 100% of a *Brevundimonas [Pseudomonas] diminuta* culture to a concentration of $10^7$ colony-forming units/cm² of filtering surface and to a minimum pressure of 50 psi; depending on the manufacturer, the nominal size of the membrane pores is 0.22 µm or 0.2 µm[187]). |
| 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. |

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

## 9. LIST OF TABLES

## 10. APPENDICES

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## 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 condition (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 personnel training and competency assessment program, including the 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 the characteristics of compounding hazardous sterile preparations | |
| | **3.** | **Delegation of activities** | |
| | 3.1 | Delegation of technical activities to persons other than pharmacists/pharmacy technicians | |
| | **4.** | **Facilities and equipment** | |
| | 4.1 | Access to controlled areas | |
| | 4.2 | Facilities and equipment 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, including the characteristics of compounding hazardous sterile preparations (e.g., certification of rooms and devices, calibration, maintenance of pre-filters and HEPA filters, pressure verification) | |
| | 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 date of products used in a preparation | |
| | 4. | Determining beyond-use date 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 hazardous compounded sterile preparations | |
| | 12. | Labelling of hazardous compounded sterile preparations | |
| | 13. | Storage of final hazardous compounded sterile preparations | |
| | 14. | Recording of preparations in the patient's file | |
| | 15. | Transport and delivery of final hazardous compounded sterile preparations (to the patient, patient care units or 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, 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 of 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 a recent edition of the following publications available:**

- 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: http://www.asstsas.qc.ca/publications/publications-specialisees/guides-de-prevention/prevention-guide-safe-handling-of-hazardous-drugs.html
- 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; 2008-2009 (contains all USP chapters useful to pharmacists, including General Chapter <797>: Pharmaceutical Compounding — Sterile Preparations).

### B. Supplemental references

#### 1. GENERAL TEXTS ON STERILE PREPARATIONS

**Volumes**

- Buchanan EC, Schneider PJ. *Compounding sterile preparations*. 3rd ed. Bethesda, MD: American Society of Health-System Pharmacists; 2009. 481 pages.

**Periodicals**

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

**Websites: associations and agencies**

- ASHP Sterile Compounding Resource Center: www.ashp.org/compounding
- Pharmacy Compounding Accreditation Board: www.pcab.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 pharmaceutics database* [electronic database].Cashiers, NC: TriPharma Communications. Updated regularly.

#### 3. REFERENCE TEXT: PHARMACOKINETICS

DiPiro JT, Spruill WJ, Wade WE, Blouin RA, Pruemer JM. *Concepts in clinical pharmacokinetics*. Bethesda, MD: American Society of Health-System Pharmacists. About 250 pages.

## APPENDIX 3 TRAINING OF COMPOUNDING PERSONNEL AND CLEANING AND DISINFECTING PERSONNEL

### A. Training of compounding personnel

| # | ELEMENTS TO COVER IN TRAINING | | | |
|---|---|---|---|---|
| 1. | **FOR THE COMPOUNDING OF HAZARDOUS STERILE PREPARATIONS** | **PH** | **PT** | **PA** |
| 1.1 | Know the relevant federal/provincial/territorial legislation and regulations related to pharmacy compounding, as well as other governing standards, guides or guidelines. | X | X | |
| 1.2 | Know and apply all policies and procedures related to the pharmacy compounding of sterile preparations, especially those related to hand hygiene, garbing, aseptic techniques, airflow principle, facilities (ISO Classes 5 and 7 ), material, equipment, behaviour of personnel in compounding rooms, forms and logs to be completed, labelling, storage, distribution to patients, quality controls (sampling) and maintenance and disinfecting of sterile preparation compounding areas. | X | X | X |
| 1.3 | Know physical and chemical properties such as stability, physical-chemical compatibility and incompatibility, osmolality and osmolarity. | X | | |
| 1.4 | Know pharmaceutical and medical abbreviations. | X | X | X |
| 1.5 | Know and understand the importance of particulate and microbial contamination. | X | X | X |
| 1.6 | Perform pharmacy sterile-product compounding tasks meticulously, precisely and competently. | X | X | X |
| 1.7 | Know and apply appropriate aseptic techniques in the workplace. | X | X | X |
| 1.8 | Know the operation and correct use of equipment, materials and automated devices available for the sterile preparations to be compounded. Know how to calibrate the devices used. | X | X | X |
| 1.9 | Be able to recognize errors in the compounding technique of compounding personnel. | X | X | |
| 1.10 | Have a good command of the pharmaceutical calculations required to compound sterile preparations. | X | X | X |
| 1.11 | Understand the importance of and apply accurate measurements. | X | X | X |
| 1.12 | Apply disinfection measures for sterile-product compounding rooms, facilities and materials. | X | X | X |
| 1.13 | Know the data to be monitored in controlled areas (temperature, pressure, humidity) and document in the appropriate logs. Know and apply the corrective measures to be applied when irregularities are found. | 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 and 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** | **PH** | **PT** | **PA** |
| 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 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 (i.e., receive, unpack, store and deliver hazardous products). | X | X | X |
| 2.7 | Know and apply 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 |
|---|---|---|---|---|
| 2. | **FOR CLEANING AND DISINFECTING THE AREA USED FOR COMPOUNDING HAZARDOUS STERILE PREPARATIONS** | | | |
| 2.1 | Know, correctly perform and document cleaning and disinfecting tasks for the general area for compounding of hazardous sterile preparations. | X | X | X |
| 2.2 | Know and use personal protective equipment specifically for handling hazardous products. | X | X | X |
| 2.3 | 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<br><br>Or<br><br>Hospital XYZ pharmacy department | **Procedure # _____**<br><br>**Revised: Yes ☐ No ☐**<br><br>**Approved by_____ Date _____**<br><br>**Effective date: _____** |
|---|---|
| **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.

☐ Sterile Compounding Supervisor
☐ Pharmacist
☐ Pharmacy technician
☐ Pharmacy Assistant
☐ Cleaning and disinfecting personnel
☐ 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 decision, 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:** _____(dd/mm/yyyy)

**Revised by:** _____, pharmacist **Date:** _____ (dd/mm/yyyy)

**Revision:** **Full** ☐ **Partial** ☐ **Amended version:** **Yes** ☐ **No** ☐

**Change made:**

**Revised by:** _____, pharmacist **Date**:_____ (dd/mm/yyyy)

**Revision:** **Full** ☐ **Partial** ☐ **Amended version:** **Yes** ☐ **No** ☐

**Change made:**

**APPENDIX 5 - MINIMUM INDICATORS FOR CERTIFICATION OF CONTROLLED AREAS, CONTAINMENT PRIMARY ENGINEERING CONTROLS**

**Note: The following appendix lists the responsibilities of the certifier, a person engaged to certify sterile-product compounding rooms, containment primary engineering controls (C-PECs). This information is provided for the benefit of sterile compounding supervisors, to allow them to assess the services provided during the certification of areas and equipment in their respective pharmacies.**

| **I. Before certification** | |
|---|---|
| ▪ Ideally meets the client (sterile compounding supervisor) to discuss the certification process; during the meeting, the certifier<br>✓ asks whether problems have occurred since the last certification;<br>✓ asks whether there are any concerns about the operation of rooms or devices (C-PECs).<br>▪ Knows the PPE required to enter a controlled room and the garbing sequence.<br>▪ Knows the required procedure for hand and forearm hygiene before putting on gloves and entering a controlled room. | |
| **II. General precertification requirements** | |
| ▪ Cleans and disinfects all equipment brought into the controlled rooms;<br>▪ Performs certification of the controlled rooms, C-PECs following the steps and methods recommended by the applicable standards;<br>▪ Uses the applicable standards for certification (*see* Appendix 6);<br>▪ Uses the devices required by the standards (*see* Appendix 6);<br>▪ Uses calibrated devices that are in good condition;<br>▪ Knows the standards to be used for certification and knows how to apply them;<br>▪ Wears the appropriate PPE to enter and work in the compounding rooms for hazardous sterile preparations;<br>▪ Is familiar with the products used, especially if they are hazardous;<br>▪ Does not touch hazardous products; if touching a hazardous product is required, asks qualified personnel to do so;<br>▪ If applicable, sets up a protective wall (plastic or other) before opening the device, to limit contamination of the controlled room by hazardous products;<br>▪ Performs the work meticulously and professionally. | |

| III. Certification steps (certification of all areas and devices needs to be directed by CETA guidance documents CAG-002,003, and 008) | |
|---|---|
| 1. **Certification of controlled areas** | |
| ▪ Uses the criteria of standard CETA CAG-002 and CETA-CAG-008 for the certification of the clean room;<br>▪ Measures non-viable particles;<br>▪ Measures the volume of air supply or the velocity for each HEPA filter in the room;<br>▪ Measures the air velocity profile for each terminal or line HEPA filter (as applicable) in the controlled room, if the air volume for the HEPA filter cannot be measured;<br>▪ Calculates the air volume for the HEPA filter, if the velocity profile was measured;<br>▪ Verifies the integrity of the HEPA filter with a photometer;<br>▪ Verifies temperature;<br>▪ Verifies humidity;<br>▪ Verifies sound (noise) level;*<br>▪ Verifies light level;*<br>▪ Verifies the behaviour of the room and its equipment using smoke tests;<br>▪ Ensures that the doors to each room are fully closed when measuring pressure differentials between rooms;<br>▪ Obtains the dimensions of the room and its total volume of air supply, to allow calculation of number of air changes per hour.<br>* **Note:** The frequency of certain verifications, such as sound and light levels, may vary depending on needs and agreements. | |
| 2. **Certification of BSC** | |
| ▪ Certifies the BSC according to CETA CAG-003 and CETA CAG-005;<br>▪ Takes readings to measure the velocity of the air supply of a BSC according to CETA CAG-003 and CETA CAG-005;<br>▪ Proceeds with the count of non-viable particles;<br>▪ Verifies the count of non-viable particles 0.5 µm in diameter;<br>▪ 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 and 1 $m^3$ samples per reading point (the acceptable limit is 3520 particles). | |
| | |

| | |
|---|---|
| ▪ | |
| **3. Certification of CACI** | |
| ▪ Certifies devices according to CETA CAG-002-2006 (Compounding Isolator Testing Guide);<br>▪ Certifies, using all the tests required by CETA CAG-002-006), For examples:<br>✓ Airflow test<br>✓ Verification of internal pressure<br>✓ Verification of installation site<br>✓ Verification of HEPA filter<br>✓ Containment integrity and enclosure leak test<br>✓ Recovery time test<br>✓ Smoke test<br>✓ Test of preparation entry and output<br>✓ Count of non-viable particles | |
| **IV. After certification** | |
| ▪ Answers questions and requests from the sterile compounding supervisor related to the certification and its procedure;<br>▪ Does the required quick cleaning of rooms and devices;<br>▪ Groups all waste contaminated by hazardous products and disposes of it as hazardous waste in the appropriate containers;<br>▪ Verifies that all certification labels are correctly printed and affixed;<br>▪ Provides the sterile compounding supervisor with a preliminary report (recommended but not mandatory) in writing or, at a minimum, verbally;<br>▪ Submits a final certification report that includes all information required by pharmacy regulatory authorities to confirm certification;<br>▪ Submits recent calibration certificates for the devices used in the certification, attached to the final certification report. | |

CAI = compounding aseptic isolator; CACI = compounding aseptic containment isolator; CETA = Controlled Environment Testing Association; HEPA = high-efficiency particular air; NSF = NSF International (public health and safety organization); PPE = personal protective equipment.

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

| TARGET | CERTIFICATION STANDARDS | CERTIFICATIONS |
|---|---|---|
| **Biological safety cabinet, Class II, type B2**<br><br>**(For certification of other types of BSC, please refer to the standards.)** | • CETA CAG-003 and CAG-005<br>• NSF Standard 49-2012: Biological Safety Cabinetry: Design, Construction, Performance and Field Certification<br>• ISO 14644-1 | Class II, type B2 BSC certification includes steps carried out:<br><br>In accordance with CETA CAG-003 and CAG-005<br>• Measurement of air supply profile<br>• Measurement of air intake velocity<br>• Smoke test<br>• HEPA filter integrity test<br>• Verification that interlock system (between discharge probe and air supply motor) is working properly (for Class II, type B2 BSC)<br>• Verification of device calibration (less than 20% air loss in 15 seconds) (for Class II, Type B2 BSC)<br>• Count of non-viable particles (0.5 µm) in operational (dynamic) state; at-rest state is optional<br>• Measurement of air intake velocity<br><br>Equipment used:<br>• Particle counter<br>• Thermal anemometer<br>• Smoke machine and aerosol generator<br>• Photometer<br>• Direct volume measurement device |

| | | |
|---|---|---|
| **Compounding aseptic containment isolator** | • CETA CAG-002-2006: Compounding Isolator Testing Guide | <u>Isolator certification includes steps carried out according to CETA/CAG-002-2006.</u><br><br><u>All tests required by CETA, example:</u><br>• Airflow test<br>• Verification of internal pressure<br>• Verification of installation site<br>• Verification of HEPA filter<br>• Containment integrity and enclosure leak test<br>• Recovery time test<br>• Smoke test<br>• Test of preparation entry and output<br>• Count of non-viable particles<br><br><u>Equipment used:</u><br>• Thermal anemometer<br>• Pressure measurement device (in inches of water or pascals)<br>• Tools for adjusting alarms<br>• Smoke machine<br>• Photometer<br>• Particle counter (small)<br>• Aerosol generator<br>• Chronometer |
| | | |
| **Clean room for the compounding of sterile preparations and controlled areas** | • CETA CAG-003: Certification Guide for Sterile Compounding Facilities<br><br>• NEBB Procedural Standards for Certified Testing of Clean rooms<br><br>• IEST-RP-CC-006.3: Testing Clean Rooms<br><br>• ISO 14644-1 (section on number of particles, particle counters, and sampling plan and methods). | <u>Certification of controlled areas and rooms includes the following steps in accordance with CETA CAG-003:</u><br>• Count of non-viable particles in operational (dynamic) state<br>• Certification of HEPA filter<br>• Verification of terminal or line HEPA filter<br>• Measurement of pressure differential between controlled rooms<br>• Verification of air changes per hour (by measuring volumes of air or room velocity)<br>• Verification of behaviour of rooms and equipment using smoke tests<br>• Temperature verification<br>• Relative humidity verification |

| | | |
|---|---|---|
| | | • Measurement of luminosity<br>• Measurement of noise level (sound)<br><br><u>Equipment used:</u><br>• Particle counter<br>• Tripod for the room<br>• Tripod for the LAFW or BSC<br>• 0.3-µm filter (for cleaning)<br>• “Tent” to capture air volume<br>• Thermal anemometer<br>• Smoke machine<br>• Photometer<br>• Pressure measurement device (in inches of water or pascals)<br>• Thermometer<br>• Hygrometer<br>• Light meter<br>• Sound level meter |

ANSI = American National Standard Institute; CETA = Controlled Environment Testing Association; IEST = Institute of Environmental Sciences and Technology; NEBB = National Environmental Balancing Bureau

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

Information on certifiers can be found on the following websites: http://www.nsf.org (select the following options: regulatory resources / NSF certification / search certified products and systems / Class II Biosafety Cabinet Field Certifiers / search by country) and http://www.nebb.org (Certified firms/Directory of firms/NEBB certified firm/Search by country/Canada.

## 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:

- 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 controls**

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

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

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

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

**Packaging**

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

**Stability and storage**

Specify the preservation requirements of the compounded sterile preparation.

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

Indicate the references used to determine shelf life.

| **Labelling** | **Sample label** |
|---|---|
| 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 | **Name of preparation:**<br><br>**Date when preparation was made:**<br>**Lot:**<br>**Quantity prepared:**<br>**Beyond-use date:**<br>**Shelf life:**<br>**Verified by:** |
| B) When dispensed to a patient | **Customer label**<br><br>In addition to the legally mandated information, add:<br><br>- lot number of compounded sterile preparation<br>- beyond-use date<br>- precautions and other patient information leaflet |

**Training**

Indicate the training that personnel must undergo before the specific sterile compounding procedure is implemented.

**References consulted:**

Indicate the source of the specific sterile compounding procedure.
Indicate any documentation supporting the stability of the final compounded sterile preparation.

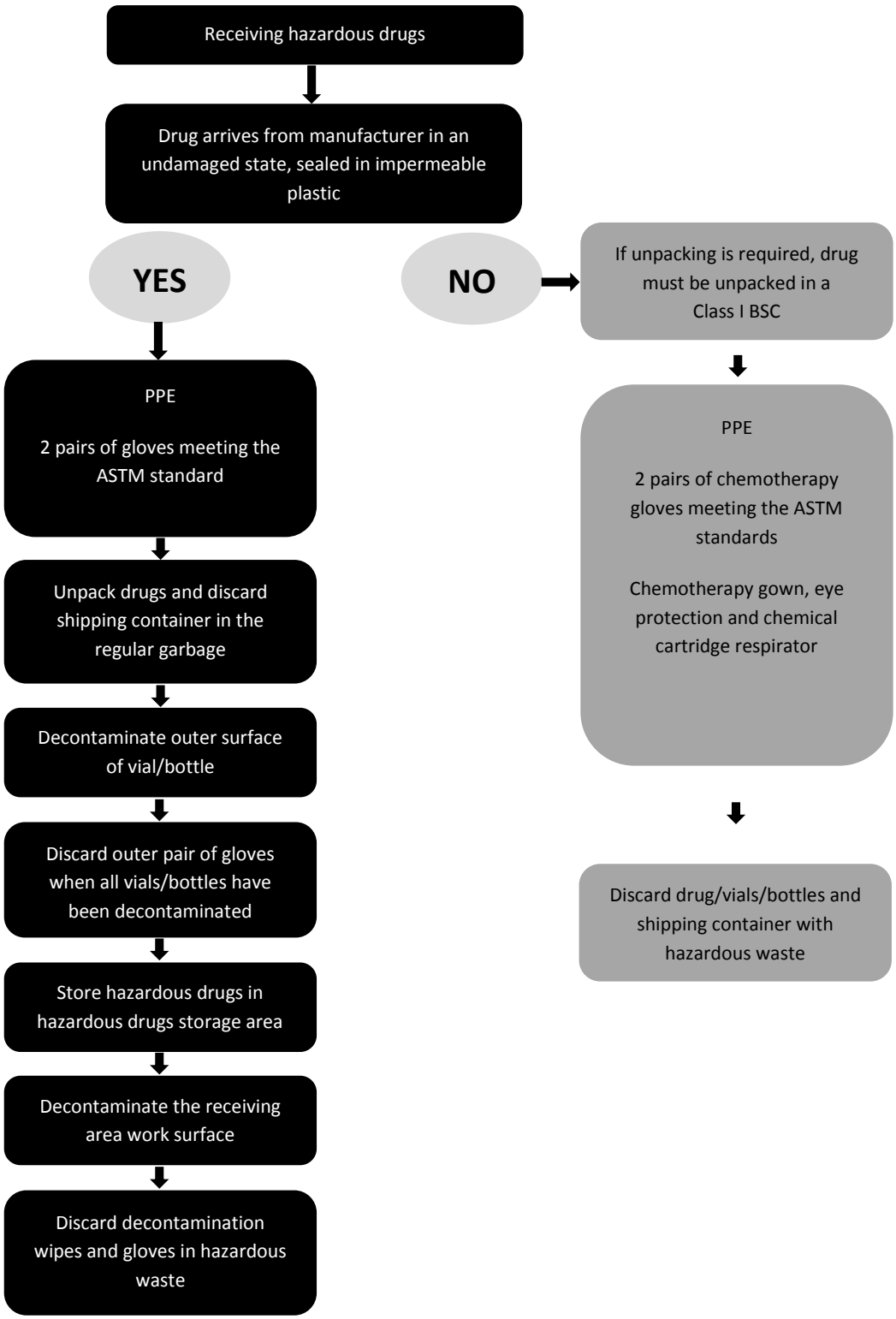
| | |
|---|---|
| **Preparation data sheet history No.:** | |
| **Date drafted:** (dd/mm/yyyy) | **Drafted by:** |
| **Revised:** (dd/mm/yyyy)<br><br>**Change made:** | **Revised by:**<br><br>**Version number changed:** ☐ **YES** ☐ **NO** |
| **Revised:** (dd/mm/yyyy)<br><br>**Change made:** | **Revised by:**<br><br>**Version number changed:** ☐ **YES** ☐ **NO** |

## 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, and more frequently if necessary (e.g., if a large number of units is prepared). |

## APPENDIX 9 PROCEDURE EXAMPLE

***Receiving, unpacking and storing hazardous products***



## APPENDIX 10 TEMPERATURES FOR DIFFERENT TYPES OF STORAGE

| | Temperature range |
|---|---|
| Freezing | –25°C to –10°C* |
| Refrigeration (cold) | 2°C to 8°C* |
| Temperature (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 pharmacists and pharmacy technicians need to have in place.

| **Incident/accident* reporting and follow-up** | | |
|---|---|---|
| **Reporting an incident ☐ accident ☐** | | |
| **General information** | | |
| Date and time of incident/accident: | Reported by: | |
| Name of patient affected, if applicable: | Full address:<br><br>Phone number: | |
| Pharmacy personnel involved: | | |
| **Information about incident/accident** | | |
| (Summary of the situation and consequences) | | |
| **Disclosed to the patient concerned: ☐** | | |
| **Name of pharmacist responsible for follow-up:** | | |
| **Analysis of causes** | | |
| Causes:<br>(Identify causes of the problem) | Options for corrections or changes:<br>(Assess potential corrections or changes to be made) | Corrections or changes chosen:<br>(Indicate the corrections or changes to be made) |
| **Action plan** | | |

| **Actions**<br>(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<br>(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, professional concerned or 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, professional concerned or third party, but which has 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 | • Every 6 months<br>• When the controlled area is installed<br>• When new equipment is installed<br>• When rooms or equipment are maintained or repaired<br>• When a contamination problem is identified<br>• 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:<br>- Viable and non-viable particles, air and surfaces<br>- According to a sampling plan | • Every 6 months (more frequently at the start of the quality assurance program)<br>• When the controlled area is installed<br>• When new equipment is installed<br>• When the controlled area or equipment is repaired or maintained (e.g., high-efficiency particulate-air filter changed)<br>• When a contamination problem is identified<br>• When investigation of a contamination problem or non-compliance in the aseptic preparation process requires exclusion of malfunctioning facilities<br>• According to an internal verification program |

| | | |
|---|---|---|
| | Verification of temperature and humidity in controlled areas | • Once a day |
| | Pressure differential between controlled areas | • Continuous reading and notification system to prevent non-compliance<br>• Periodic verification (once a week) by the sterile compounding supervisor<br>• Notification system (if reading is not continuous, assign personnel to verify and record the differential twice a day) |
| | | |
| **EQUIPMENT** | Certification of C-PEC | • Before first use<br>• Every 6 months<br>• When new C-PEC is installed<br>• When C-PEC is repaired or maintained<br>• When a contamination problem is identified<br>• 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) | • Once a day (if unit has a built-in reading device)<br>• Twice a day (if unit has no built-in reading device) |
| | Operational indicators of C-PEC and other devices used (e.g., automated compounding device) | • Verified daily before use<br>• Verified continuously by personnel |
| | Sampling of C-PEC under operational (dynamic) conditions:<br>- Viable and non-viable particles, air and surfaces<br>- According to a sampling plan | • Every 6 months (more frequently at the start of the quality assurance program)<br>• When a new C-PEC is installed<br>• When the C-PEC is maintained or repaired<br>• When a contamination problem is identified<br>• When investigation of a contamination problem or non-compliance in the aseptic preparation process requires exclusion of malfunctioning equipment<br>• According to an internal verification program |
| | | |

| | | |
|---|---|---|
| **PERSONNEL** | Competency assessment | • At initial qualification: theoretical and practical aspects<br>• At periodic qualifications: theoretical and practical aspects<br>• When assessing incidents and accidents<br>• When a contamination problem is identified |
| | Gloved fingertip sampling | • At initial qualification: theoretical and practical aspects<br>• Once a year for low and medium risk compounding<br>• Every six months for high risk compounding<br>• When assessing incidents and accidents<br>• When a contamination problem is identified |
| | Media fill tests | • At initial qualification: theoretical and practical aspects<br>• Once a year for low and medium risk compounding<br>• Every 6 months for high risk compounding<br>• When assessing incidents and accidents<br>• When a contamination problem is identified |
| | | |
| **FINAL COMPOUNDED STERILE PREPARATION** | Verification of compounding protocols (usage and maintenance) | • In accordance with the quality assurance program |
| | Verification that preparation matches prescription | • In accordance with the quality assurance program |
| | Verification of label compliance | • In accordance with the quality assurance program |
| | Entry in logs | • In accordance with the quality assurance program |
| | | |

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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 July 2014.


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