MPhA Standard of Practice # 8:

A pharmacist shall be responsible for all extemporaneous compounding, which shall be done according to established procedures and legal requirements.

1.0 PURPOSE:
To set forth procedures and controls to assist in assuring the quality of compounded products.

2.0 SCOPE:
This guideline/standard is intended to include all non-sterile and sterile products prepared from raw materials, and parenteral products prepared from commercially available injectable products.

3.0 DEFINITIONS:
Please refer to CSHP, NAPRA and Health Canada Policy on Manufacturing and Compounding POL-0051

4.0 PRINCIPLES:
Pharmacists have the knowledge and skill to properly prepare extemporaneous compounds. Notwithstanding that, a pharmacist must:
   o understand the risks associated with the preparation of specific products and their personal professional limitations, and
   o have the appropriate equipment and facilities for the task.
Alternate options could include:
   • referring the patient to another pharmacy with the appropriate skills and equipment for that product,
   • contacting the prescriber and suggesting an alternative product, or
   • consult with colleagues to evaluate options.
The onus is ultimately on the pharmacist to ensure the proper preparation.

In the preparation of compounded products, Manitoba has adopted by reference the guidelines of the Canadian Society of Hospital Pharmacists (CSHP), NAPRA and the Health Products and Food Branch Inspectorate Policy on Manufacturing and Compounding Drug Products in Canada POL-0051. The documents are listed in the attached appendices list.

5.0 PHARMACY STANDARDS (Compounding)
Pharmacies engaging in compounding shall have a specifically designated area for the orderly placement of equipment and materials to be used. The compounding area for sterile products shall be separate and distinct from the area used for compounding of non-sterile drug products. The area designated for compounding shall be:
   a) maintained in a clean, sanitary condition,
   b) permit effective cleaning of all surfaces
   c) conducive to the orderly cleaning of all surfaces
   d) in a good state of repair to minimize the potential (for contamination of the drug or the addition of any extraneous material to the product.
6.0 RAW MATERIALS (Compounding):
Bulk drugs and other materials used in the compounding of drugs must be stored in adequately labeled containers in a clean, dry area or, if required, under proper refrigeration. Drug components shall be received, handled and stored in a manner to prevent contamination of product and staff in accordance with official compendia WHMIS Guidelines. Material Safety Data Sheets (MSDS) are available from manufacturers with detailed information on safe use and employee protection.

7.0 PROCEEDURES:
To assure reasonable uniformity and integrity of compounding products, written procedures shall be established and followed, that describe the tests or examinations to be conducted on products being compounded (ie. compounding of capsules). Such procedures that may be responsible for causing variability in the final product include, but are not limited to:
   a) capsule weight variation
   b) sufficient mixing of ingredients to ensure uniformity
   c) clarity, completeness or pH of solutions

8.0 DOCUMENTATION:
Extemporaneous preparation documentation should be placed on a dispensing worksheet or on the reverse side of the prescription. The following information should be included:
   a) patient name,
   b) compound name and strength,
   c) name, manufacturer and lot no. of each raw material used,
   d) formulation stating quantity and percent weight or volume of each raw material,
   e) source of formula, if available,
   f) description of each step and equipment used in the compounding process,
   g) expiry date
   h) storage requirements
   i) prepared by/checked by initials
   j) use of product by patient
   k) usual dose range
   l) advice for the patient
   m) specific packaging requirements
   n) sample label, including auxiliary labels when applicable,

9.0 STERILE COMPOUNDING:
Manitoba has adopted the guidelines of the Canadian Society of Hospital Pharmacists (CSHP) for the preparation of sterile products and the handling and disposal of hazardous products for all areas of pharmacy practice in Manitoba. They are noted in the attached appendices:

10.0 DOCUMENTS ACCEPTED BY REFERENCE:
Appendix 1: Sterile Compounding Comparison of Risk Categories;
Appendix 2: Sterile Compounding Reference List
Appendix 3: Refer to NAPRA: Guidelines to Pharmacy Compounding
Appendix 4: Refer to Health Canada: Policy on Manufacturing and Compounding Drug Products in Canada POL-0051"
Guidelines for Drug Packaging and Labelling for Manufacture”
Appendix 5: Refer to CSHP: “Guidelines for Bulk Compounding of Products in Hospitals
Appendix 6: Refer to CSHP: “Repackaging Products in Health Care Facilities”
Appendix 7: Refer to CSHP: “Guidelines for Unit Dose & IV Admixture Drug Distribution”
Appendix 9: Refer to CSHP: “Guidelines for the Handling and Disposal of Hazardous Pharmaceuticals (Including Cytotoxic Drugs)
Appendix 10: Refer to CSHP: “Nonsterile Compounding: Guidelines for Healthcare Facility Pharmacies”

MPHA Extemporaneous Compounding: Feb 1, 2010
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<td>Sterile drug products transferred from vials or ampoules</td>
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<td>into sterile final containers with syringe and needle</td>
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<td>Sterile drug products transferred into sterile elastomeric</td>
<td>Single patient syringes without preservatives</td>
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<td>infusion containers with aid of mechanical pump and</td>
<td>used in 28 hours</td>
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<td>appropriate sterile transfer device, with or without</td>
<td>Batch prefilled syringes with</td>
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<td>and amino acid injection via gravity transfer into sterile</td>
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<td>empty containers, with or without addition of sterile</td>
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<td>one drug product, with evacuation of air from</td>
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<td>Ambulatory pump reservoirs prepared for multiday ambient</td>
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<td>Injectable morphine solutions prepared from nonsterile</td>
<td>Alum bladder irrigations</td>
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<td>morphine substance and suitable vehicles</td>
<td>Morphine injections made from</td>
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<td>Sterile nutritional solutions prepared from nonsterile</td>
<td>powder or tablets eg for PCA</td>
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<td>ingredients, with initial mixing in non-sealed or nonsterile</td>
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<td>TPNs sterilized by final filtration</td>
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</tbody>
</table>

Note: USP section 1206 has been revised and is now Section 797
Appendix 2: Reference List

1. American Society of Health-System Pharmacy
7272 Wisconsin Avenue Bethesda, MD 20814
Phone: 301-657-3000
Website: www.ashp.org

2. Canadian Pharmacists Association 1785 Alta Vista Drive Ottawa, Ontario K1G 3Y6 Tel: 1-800-917-9489 or (613) 523-7877 Fax: (613) 523-0445
Website: www.cdnpharm.ca

3. Canadian Society of Hospital Pharmacists
1145 Hunt Club Road, Suite 350
Ottawa, ON K1V 0Y3
Phone: 613-736-9733 Fax: 613-736-5660
Website: www.cshp.ca

4. U.S. Pharmacopeia
12601 Twinbrook Parkway
Rockville MD 20852 1790
Phone: 80-277-8772 or 301-81-0666
Website www.usp.org

5. Login Brothers
324 Salteaux Crescent
Winnipeg, Manitoba R3J 3T2
Phone: 800-665-1148 Fax: 800-665-0103
Website: www.lb.ca

King Guide Publications, Inc.
PO Box 10317 Napa, CA 94581
Phone: (707) 257-7573 Fax: (707) 257-7566 Website: www.kingguide.com

Reference:
CSHP Guidelines for Bulk Compounding of Products for Hospitals
CSHP Guidelines for the Preparation of Sterile Products in Pharmacies
Repackaging Products in Health care Facilities
ASHP Guidelines on Quality Assurance for Pharmacy-Prepared Sterile Products
NABP Model Rules for Sterile Pharmaceuticals
Appendix 3:
NAPRA: Guidelines to Pharmacy Compounding

Guidelines to Pharmacy Compounding

October 2006
## Guidelines to Pharmacy Compounding

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**Appendix A**

**References**
Introduction

In February of 2004, the Importation and Compounding of Animal Drugs Task Force met to discuss several issues related to the use of compounded products in Canada. It was decided that guidelines needed to be developed in collaboration with provincial pharmacy licensing bodies to describe when it is appropriate to compound and how to compound. The National Association of Pharmacy Regulatory Authorities (NAPRA) made a commitment to develop such guidelines and the Compounding Guidelines Task Force (CGTF) was formed in January 2005 to complete this initiative. The CGTF, which developed these guidelines, is made up of pharmacists from across Canada (see Appendix A) experienced in the area of compounding preparations and nominated by their provincial Pharmacy Regulatory Authority. The task force recognized that compounding is an essential part of pharmacy practice and the guidelines reflect the knowledge they felt was required to prepare a safe and appropriate product.

Once the draft guidelines were completed, they were reviewed by the NAPRA’s National Advisory Committee on Pharmacy Practice, the Council of Pharmacy Registrars of Canada, and NAPRA’s Executive Committee. The guidelines also underwent an extensive external review.

These guidelines, referred to as the Guidelines to Pharmacy Compounding, are not meant to supersede the Model Standards of Practice for Canadian Pharmacists (NAPRA, April 2003) but to enhance the area addressing compounding. (Professional Competency #4: Manage Drug Distribution)

1.0 Scope

These guidelines apply to pharmacists or their delegates in the preparation of all extemporaneous products. The CGTF based these guidelines on the following performance indicators for pharmacists fulfilling this role:

1. Have accurate knowledge and expertise to compound preparations;
2. Confirm the need for a compounded product;
3. Maintain access to contemporary equipment;
4. Use of quality ingredients and procedures;
5. Appropriate labeling;
6. Suitable containers for each unique product;
7. Safe and acceptable storage; and
8. Documentation to ensure accurate checking, duplicating, and tracing.

The key elements of good compounding include qualified and trained personnel, adequate premises and space, approved compounding procedures and instructions, suitable equipment, labels and containers, and accurate documentation.

---

1 Importation & Compounding of Animal Drug Task Force, 2nd meeting notes, February 5, 2004
2.0 Definitions

2.1 Compounding

Pharmaceutical preparation of components into drug products that:

1. Are considered to be within the professional practice of pharmacy, regulated by provincial regulatory authorities in accordance with guidelines and standards that ensure the quality and safety of pharmaceuticals;

2. Involve a relationship that can be demonstrated to exist between a patient and/or:
   a) a regulated health care professional
   b) a practitioner;

3. Do not circumvent regulatory requirements including the Food and Drugs Act and the Food and Drug Regulations, the National Drug Schedules, or intellectual property legislation; and

4. Provide a customized therapeutic solution to improve patient care without duplicating a commercially available, approved product.

2.2 Manufacturing

Preparation of products:

1. Are subject to all the appropriate divisions and sections of the Food and Drugs Act and Regulations, including all applicable standards and guidelines.

2. Require a Drug Identification Number (DIN) and/or Notice of Compliance (NOC) to be sold in Canada.

3. Are produced independently of the demonstrated regulated health care professional-patient relationship or valid pharmacist-veterinarian-client-patient relationship.

4. Are required to obtain an Establishment License (EL) (Division 1A of the Food and Drugs Act and Regulations) and meet the appropriate sections of Division 2 Good Manufacturing Practices (GMP).

3.0 Personnel

3.1 Pharmacists that compound or delegate compounding activities to technical staff should have the knowledge and skills to be responsible for the preparation of the product.

3.2 Pharmacists should use their professional judgment when deciding whether they have the expertise to compound a specific product and should be aware of good compounding principles and practices.

3.3 Pharmacists unable to compound a drug product for the patient should refer the patient to a pharmacist with the ability to prepare the product.
3.4 The pharmacist should gather sufficient information to make knowledgeable decisions regarding the formulation and process of the compounding. Formulations should be accessed from a reputable source such as a peer-reviewed published journal. If no formulation is available, a formula should be completed using the pharmacist's knowledge in pharmacology, chemistry, and therapeutics.

3.5 The pharmacist should:
   a. Assist individuals requiring a compounded item;
   b. Counsel individuals on the appropriate use of the compounded product;
   c. Determine whether the product should be compounded in a sterile manner;
   d. Ensure the quality and accuracy of the ingredients;
   e. Calculate required quantities, dilutions, percentages or other pharmaceutical calculations as required;
   f. Be knowledgeable of the purpose of each ingredient in the compound and differentiate between active ingredients and excipients;
   g. Recognize the potential for incompatibilities;
   h. Determine the equipment needed to compound the product;
   i. Prepare the product in a logical, safe, and pharmaceutically elegant manner; and
   j. Document the required information to maintain accurate records.

4.0 Premises

4.1 The compounding area should be clean, sanitary, and orderly.

4.2 Premises should permit effective cleaning of all surfaces.

4.3 Premises should prevent contamination of medication and the inadvertent addition of extraneous material to the medication.

5.0 Equipment

5.1 Equipment used for compounding should:
   a. Be situated in an area that permits it to function in accordance with its intended use. Equipment should be operated in a manner that prevents contamination.
   b. Be easily and routinely cleaned to minimize the potential for contamination;
   c. Be suitable for the preparation of the desired compound; and
   d. Be kept clean, dry, and protected from contamination during storage to prevent the addition of extraneous materials.

5.2 Equipment used for measuring and weighing should be calibrated, if appropriate, on a regularly scheduled basis and documentation showing proof of calibration and servicing should be maintained in the pharmacy records.
6.0 Sanitation

6.1 The pharmacy should have a written sanitation program available to include cleaning requirements for the premises and equipment.

6.2 Written procedures detailing the minimum requirements for health and hygienic behavior of individuals performing compounding activities should be addressed in a policy manual. This should include, but not be limited to:
   a. Suitable dress (e.g. gowns, masks, gloves, footwear);
   b. Hand hygiene; and
   c. Health conditions and open lesions.

7.0 Quality Control Requirements

7.1 Ingredients

7.1.1 The pharmacist should be able to distinguish materials that require specialized handling and storage, and demonstrate safe handling techniques such as, but not limited to:
   a. Measuring or triturating in an appropriate environment;
   b. Donning the appropriate apparel; and
   c. Ensuring that personnel handling the ingredients do so in a safe manner.

7.1.2 The pharmacist should ensure the quality of the ingredients by using products with a standard designation such as:
   a. BP (British Pharmacopeia), USP (United States Pharmacopeia) or NF (National Formulary) standard of quality; or
   b. A valid lot number and beyond-use-date (if available). If expiry is not available, a date of receipt should be recorded on the raw material; or
   c. A Certificate of Analysis (C of A) for raw materials that is maintained in the records.

7.1.3 Ingredients should be selected based on:
   a. Solubility;
   b. Stability (provide an environment in which the ingredients are most likely to resist chemical change or degradation);
   c. Compatibility;
   d. Patient’s allergies, disease state, ability to administer, and other medications;
   e. Intended use;
   f. Duration of treatment;
   g. Potential drug-drug interactions;
   h. Medication administration frequency; and
   i. Route of Administration.
7.2 Record Keeping

7.2.1 Written compounding records must be available to enable the pharmacist to check all compounded medication to ensure that all compounded products can be:
   a. Replicated in formulation and production; and
   b. Retrieved in the event of a recall or adverse event.

7.2.2 Master compounding records should be written to provide an acceptable overage to compensate for ingredients lost/degraded during the process based on a recognized standard (e.g. Canadian Society of Hospital Pharmacists, United States Pharmacopeia).

7.2.3 Information documented on each product should include, but not be limited to:
   a. Name, lot number, and expiry of raw material;
   b. Quantity required and quantity actually weighed;
   c. Date of preparation and expiry;
   d. Initials/signature of compounder and/or pharmacist responsible for the preparation and checking;
   e. Written formula used;
   f. Records of stepwise operating/processing instructions;
   g. Maintenance of training records; and
   h. Any other documentation required by the provincial regulatory authority.

7.2.4 Deviations from written preparation process should be avoided. If deviations occur, the pharmacist should describe the deviation and the rationale and maintain these records for a minimum of 2 years from the date originally dispensed.

7.2.5 A yield and reconciliation should be carried out on each compounded medication.

7.2.6 At all practical times during the compounding process, materials should be labeled to prevent confusion.
8.0 Labeling

8.1 Product labels shall follow all federal and provincial requirements.

8.2 Labels of compounded products should include, but not be limited to:

   a. List of active ingredients;
   b. Prescription or identification number of the compounded product; and
   c. Estimated beyond-use-date printed at the end of the dosage duration.

9.0 Packaging

9.1 The packaging should be appropriate for the stability of the product and proper patient use.

9.2 A compounded product should not be made to look like an approved product.

10.0 Storage and Transportation

10.1 Storage and transportation instructions should be given to the patient or patient’s agent verbally and in written form.

10.2 Raw material and the dispensed product should be stored and transported in a manner that prevents the alteration to the potency, purity, and physical characteristics of the raw material.

11.0 Documentation

11.1 Records of complaints from patients and adverse events regarding compounded medications should be maintained for a minimum of two years from the date the prescription was dispensed. These complaints and adverse events should be investigated to determine the cause, and appropriate measures should be taken to prevent recurrence. Results of the investigation should be included in the records.

11.2 Suspected adverse reactions should be reported to health authorities as appropriate.
12.0 Sterile Compounding

12.1 Pharmacists engaging in sterile compounding should be knowledgeable and obtain specialized technical training in this area.

12.2 Carefully established standards for the operation of clean rooms and the preparation of sterile products should be documented in accordance with a recognized source (e.g. Canadian Society of Hospital Pharmacists).

12.3 Sterility testing shall be done according to a clearly defined standard (e.g. USP) and the product assigned an estimated expiry date.

13.0 Veterinary Medicine

13.1 Compounding health products for use in animals requires an established pharmacist-veterinarian-client-patient relationship.

13.2 Compounding of medications indicated for veterinary use should follow the same guiding principles as found in this document and Model Standards of Practice for Canadian Pharmacists (NAPRA, April 2003).

13.3 Pharmacists dispensing products intended for administration to animals bred, raised, kept, or slaughtered specifically for the purpose of producing food for human consumption and those animals, originally bred, raised, and kept for sport, leisure or other purposes, from the moment when they become destined for human consumption should be aware of relevant sections of pertinent legislation specific to that population.

13.4 Time required for the drug to be metabolized and excreted to ensure the animal is fit for human consumption should be added to the label for food producing animals or where necessary as assigned by the veterinarian prescribing the product.
Appendix A

NAPRA Compounding Guidelines Task Force Members

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<tbody>
<tr>
<td>Carolyn Carruthers</td>
<td>Saskatchewan College of Pharmacists</td>
</tr>
<tr>
<td>Kendra Day</td>
<td>Prince Edward Island Pharmacy Board</td>
</tr>
<tr>
<td>Ken Dicks</td>
<td>Newfoundland and Labrador Pharmacy Board</td>
</tr>
<tr>
<td>Peter Ford</td>
<td>New Brunswick Pharmaceutical Society</td>
</tr>
<tr>
<td>Rita Ozolins</td>
<td>Ontario College of Pharmacists</td>
</tr>
<tr>
<td>Larry Salsman</td>
<td>Nova Scotia College of Pharmacists</td>
</tr>
<tr>
<td>Larry Thorne</td>
<td>College of Pharmacists of British Columbia</td>
</tr>
<tr>
<td>Mike Wolowyk</td>
<td>Alberta College of Pharmacists</td>
</tr>
<tr>
<td>Dennis Wong</td>
<td>Manitoba Pharmaceutical Association</td>
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_NAPRA Staff Resource: Cathy Biggs (Director of Pharmacy Practice at the time of the drafting of these Guidelines)_
References


Animal Medicines Training Regulatory Authority, Code of Practice, October 9, 2000


OUR MANDATE:
To promote good nutrition and informed use of drugs, food, medical devices and natural health products, and to maximize the safety and efficacy of drugs, food, natural health products, medical devices, biologics and related biotechnology products in the Canadian marketplace and health system.

Health Products and Food Branch Inspectorate

Policy on
Manufacturing and Compounding
Drug Products in Canada

POL-0051

Supersedes:
GUI-0030 (July 30, 2001)

Date issued:
January 26, 2009

Date of implementation:
January 26, 2009

Disclaimer
This document does not constitute part of the Food and Drugs Act (Act) or the Food and Drugs Regulations (Regulations) and in the event of any inconsistency or conflict between that Act or Regulations and this document, the Act or the Regulations take precedence. This document is an administrative document that is intended to facilitate compliance by the regulated party with the Act, the Regulations and the applicable administrative policies. This document is not intended to provide legal advice regarding the interpretation of the Act or Regulations. If a regulated party has questions about their legal obligations or responsibilities under the Act or Regulations, they should seek the advice of legal counsel.

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Appendix I General Guideline on Compounding and Manufacturing Activities .......... Page 11
1.0 Purpose
The purpose of this document is:

1. To provide background information on the compounding and manufacturing of drugs in Canada;
2. To provide a policy framework to assist in distinguishing between compounding and manufacturing activities of drug products in Canada.

2.0 Scope
The scope of this policy framework covers drugs for human and veterinary use. This policy applies to all scheduled drugs regulated under the Food and Drugs Act (i.e., Schedule C (Radiopharmaceuticals), Schedule D (Biologics), Schedule F (Prescription drugs) and Schedule G (controlled substances) as well as Over the Counter drugs). Note, however, that this policy does not apply to natural health products (NHP) regulated under the Natural Health Products Regulations. A separate document will be provided by the Natural Health Products Directorate for compounding NHP.

3.0 Background
In Canada, compounding of drugs is practised primarily by pharmacists as an integral part of their profession and is regulated by the respective regulatory authorities in each province/territory. Other healthcare professionals such as physicians, veterinarians or dentists may also be involved in compounding activities when licensed to do so by the province/territory in which they practice. Drug manufacturing, on the other hand, is regulated by Health Canada under the federal Food and Drugs Act and Food and Drug Regulations. Since the maintenance and enhancement of health and safety is a responsibility that is shared between government (federal and provincial/territorial) and industry, consumers, healthcare professionals and their respective associations, it is important that the definitions for compounding and manufacturing be clearly understood so that the respective parties can fulfil their responsibilities in a coordinated and effective way.

In February 1997, a multidisciplinary workshop was held on the subject of the compounding and manufacturing of drugs in Canada. The need for clarity across roles and jurisdictions, as well as concerns related to particular products, processes and service providers were among the many issues highlighted. In July 2000, the policy document entitled Manufacturing and Compounding Drug Products in Canada was published by Health Canada following consultation with the National Association of Pharmacy Regulatory Authorities (NAPRA) and the Canadian Society of Hospital Pharmacists (CSHP).

Since the initial workshop, the compounding market has evolved greatly. The Health Products and Food Branch Inspectorate (HPFBI) held a facilitated focus group session in April 2004 to discuss the current issues on compounding, in an attempt to better differentiate compounding from the process of manufacturing. In addition, discussions also took place on developing an uniform approach to address issues that Federal and Provincial/Territorial regulators and healthcare professionals involved in compounding are confronted with. In essence, there is a need to develop a Canada wide consistency in approach to ensure that drug compounding and drug manufacturing are each regulated by the appropriate authorities.

4.0 Determination of Regulatory Responsibility/Jurisdiction
The following illustration (Figure 1.0) demonstrates the process to be followed by federal regulators, provincial/territorial regulators and healthcare professionals when dealing with jurisdictional issues related to compounding and manufacturing. Adopting this process will help develop a consistent Canada wide approach ensuring that all products and activities are appropriately regulated.
Figure 1.0 - Process in addressing Manufacturing and Compounding Issues

In essence, in circumstances where an individual cannot clearly determine whether a particular activity is considered to be manufacturing or compounding, they may contact either the Health Products and Food Branch Inspectorate or the respective provincial/territorial regulatory body (see Section 7.0 Associated Documents/Links - contact list). At that point, discussions may take place between the two jurisdictions for final determination of whether an activity is considered to be compounding or manufacturing.

Note that, in situations where the provincial/territorial regulatory authority decides that an activity does not fall within its jurisdiction, the activity is likely to be manufacturing and the parties involved must follow the federally regulated drug approval process for manufactured drugs.

4.1 Federal Jurisdiction
Manufacturers of drugs in dosage form must comply with the requirements of the Food and Drugs Act and Food and Drug Regulations including all associated standards and guidelines. In particular, manufactured drugs must be authorized for sale in Canada, meaning that the product authorization application received is reviewed for quality, safety and efficacy by Health Canada. In order to be sold in Canada, a drug will also require a Drug Identification Number (DIN) and/or Notice of Compliance (NOC) (Some products such as radiopharmaceuticals will not have a DIN). Furthermore all fabricators, packagers/labellers, distributors, importers, testers, and wholesalers will be required to obtain an Establishment Licence (EL) (Division 1A of Food and Drugs Act and Food and Drug Regulations), and meet the applicable sections of Division 2 relating to Good Manufacturing Practices (GMP) and comply with other relevant sections of the Food and Drug Regulations.

All healthcare professionals importing drug products must also comply with all applicable sections of the Food and Drugs Act and Food and Drug Regulations (C.01.005 (2) and C.01A.002(b) for importing drug products used in compounding).
All healthcare professionals compounding drug product must also comply with all relevant sections of the Food and Drugs Act including sections 3 - Prohibited advertising; 8 - Prohibited sales of drugs; 9 - Deception regarding drugs; and 11 - Unsanitary manufacture of drug.

4.2 Provincial/Territorial Jurisdiction

Healthcare Professionals
For the purpose of this Policy, Healthcare Professionals are those who are licensed to practise by their respective provincial/territorial regulatory authorities. Compounding is therefore a licensed or authorized act that falls within the scope of the practice of the professions such as pharmacy and medicine/dentistry/veterinary medicine or other healthcare professionals. Healthcare professionals who are engaged in compounding must comply with applicable provincial/territorial/federal regulations and their standards for these services. The responsibility for risk arising from compounding activities is assumed by licensed healthcare professionals in the treatment and servicing of their patients/clients.

The licensing of hospital pharmacies varies from province/territory to province/territory and may also depend if drug products are supplied only within the hospital or also to outpatients and third parties. The appropriate provincial/territorial regulatory authority should be consulted for additional information.

The use of compounded drugs in food animals is discouraged and the veterinarian is solely responsible for establishing an appropriate withdrawal time when using compounded drugs. Veterinarians should be aware that Canadian global Food Animal Residue Avoidance Databank (gFARAD) will not provide advice on withdrawal period for compounded drugs.

5.0 Policy Statement
This policy document is intended to embody the following guiding principles (key concepts are shown in bold):

General Guiding Principles

• Compounding must be a legitimate part of the practice of regulated healthcare professionals and must not be used as a means to bypass the federal drug review and approval system.
• All drug compounding and manufacturing activities performed are to be regulated and fall under either the federal or the provincial/territorial jurisdiction.
• The distinguishing between compounding and manufacturing activities is made on a case-by-case basis.

5.1 Compounding
Factors to be considered when assessing whether an activity is compounding:

a) Healthcare professionals who provide compounding related services and products to patients/clients must be able to demonstrate that a patient-healthcare professional relationship exists.

b) Activity is regulated and facility may be inspected by provincial/territorial regulatory authorities.

c) It is expected that healthcare professionals who compound products will have appropriate risk management processes in place to manage risks associated with the compounded product and the workplace (facilities, safety etc.), in line with the standards set by their provincial/territorial regulatory bodies (for example but not limited to the toxicology, pharmacology, therapeutic value, stability, adverse reactions, labelling requirements etc. of the compounded product).

d) A pharmacy may prepare drugs in very limited quantities, in anticipation of a prescription. For the purpose of this Policy, preparation involves compounding or repackaging of multiple units, not for immediate use, in a single process, by the same operator in accordance with a standardized batch preparation procedure.
e) Compounding should only be done if there is a **therapeutic need** or **lack of product** availability and should not be done solely for economic reasons for the healthcare professionals.

f) The compounded product must provide a **customized therapeutic solution** to improve patient care without duplicating an approved drug product.

g) When there is a **shortage or no supply of a commercially** available product and the healthcare professional has determined a medical need for this product, the product may be compounded during the period of shortage or no supply only.

h) Drugs should not be compounded in order to be sold to **third parties** who will in turn sell/deliver to patients outside of their defined patient-healthcare professional relationship (see definition of “sell”). Pharmacists that do not provide specific compounding services may contract this activity to another pharmacist who provides this type of specific compounding service.

i) Compounding of **clinical trial drugs** is only permitted if this activity is authorized in the clinical trial application or experimental or investigational authorization.

j) Product should be produced from an **authorized drug** or Active Pharmaceutical Ingredient (API) used in an authorized drug for use in Canada or listed in a **recognized Pharmacopoeia** (USP, PhEur, PhF, PhJ, BP, CF, NF, Codex - Schedule B Food and Drugs Act.)

k) Those engaged in sterile compounding should be knowledgeable and obtain specialized technical training in this area (The Canadian Society of Hospital Pharmacists as well as United States Pharmacopeia (USP) have developed guidelines for the preparation of sterile preparations). Compounding of **sterile products** is only permitted in hospitals or other practice settings where carefully established standards for the operation of clean rooms and the preparation of sterile products are in place and documented, in accordance with a recognized source. The products are dispensed directly to patients or to those who administer to patients, and are operating within a demonstrated patient-healthcare professional relationship. Pharmacists may delegate some of the compounding responsibilities to pharmacy technicians if they are adequately trained in compounding sterile products or if the provincial/territorial laws authorize it.

l) Pharmacists in hospitals providing compounding **services to other hospitals** should be within the same province, and operate under the same hospital management board (ie. inter-hospital transfer, where the hospital may be composed of several facilities at different locations).

m) The compounded product must comply with all relevant sections of the **Food and Drugs Act** including sections 3 - Prohibited advertising; 8 - Prohibited sales of drugs; 9 - Deception regarding drugs; and 11 - Unsanitary manufacture of drug.

n) The expiration date of the compounded product is based on known stability data. If stability data is not available, the expiration date should be short, usually limited to the duration of the prescription or use.

### 5.2 Manufacturing

An activity will be considered manufacturing in the following circumstances:

a) Healthcare professionals who cannot demonstrate that a **patient-healthcare professional relationship** exists.

b) Producing an identical product that is **already commercially available**, unless there is a shortage (see section on compounding).

c) **Producing or selling** the product by a **third party**.

d) Healthcare professionals who produce products intended for **distribution or sale outside** the demonstrated patient-healthcare professional relationship.

e) Producing products made in such a **scale, time and frequency** to fall outside of a patient-healthcare professional relationship.

f) Clinical trial application, experimental or investigational authorization does not specify authorization to compound **clinical trial drugs**.
g) Producing a drug product that requires only minor modification prior to direct administration when such modification amounts to mere directions for use. Examples of such include the addition of liquid to a powder or adding a powder to animal drinking water. Compounding does not include mixing, reconstituting, or any other manipulation that is performed in accordance with the directions for use on an approved drug’s labelling material (Aside added: “within the normal practice of pharmacy”).

h) **Repackaging** commercially available drugs in finished dosage form outside the normal dispensing activities within the practice of pharmacy.

General guidelines on compounding and manufacturing activities is summarized in Appendix I.

For additional information, contact the appropriate provincial/territorial professional regulatory authority or Health Products and Food Branch Inspectorate in Ottawa. Refer to section 7.0 Associated Documents/Links for a complete list of College of Pharmacists and Health Canada website links.

6.0 **Definitions**

**Active Pharmaceutical Ingredient (API):**
Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body. *(ICH Q7)*

**Anticipation of a prescription:**
Pharmacies may prepare drugs in very limited quantities before receiving a valid prescription, provided they can document a history of receiving valid prescriptions that have been generated solely within an established patient-healthcare professional relationship, and provided further that they maintain the prescription on file as required by provincial law.

**Compounding:**
Health Canada considers compounding to be the following:
The combining or mixing together of two or more ingredients (of which at least one is a drug or pharmacologically active component) to create a final product in an appropriate form for dosing. It can involve raw materials or the alteration of the form and strength of commercially available products. It can include reformulation to allow for a novel drug delivery. Compounding does not include mixing, reconstituting, or any other manipulation that is performed in accordance with the directions for use on an approved drug’s labelling material (Aside added: “within the normal practice of pharmacy”).

For other definitions of compounding, see Section 7.0 Associated Documents/Links (USP, NAPRA, QCP, NSCP).

**Customized Medication:**
A formulation resulting from the combination of drugs or, APIs and/or non-medicinal ingredients that meets the patient’s or animal’s specific therapeutic needs.

**Patient-Healthcare Professional Relationship:**
A relationship that can be demonstrated to exist between a patient and a regulated healthcare professional in which a professional service is provided. When the relationship involves an animal, a valid veterinarian-client-patient relationship (VCPR) is required.
Healthcare Professional:
A person lawfully entitled under the laws of a province or a territory to provide health services in the place in which the services are provided by that person including a pharmacist, dentist, medical practitioner or a veterinarian.

Patient:
An individual or animal with unique requirements receiving medical treatment distinct from a group.

Pharmacist:
An individual who (a) is registered or otherwise authorized under the laws of a province or territory to practise pharmacy; and (b) is practising pharmacy in that province.

Prescription:
An order given by a practitioner directing that a stated amount of any drug or mixture of drugs specified therein be dispensed for the person named in the order (Food and Drug Regulations C.01.001).

Repackaging:
Subsidizing or breaking up a manufacturer’s original package of a drug for the purpose of dividing and assembling the drug in larger or smaller quantities for redistribution or sale by retail.

Sell:
Includes offer for sale, expose for sale, have in possession for sale and distribute, whether or not the distribution is made for consideration. (Food and Drugs Act)

Third Party:
Any individual, organization, or company outside of a patient-healthcare professional or valid veterinarian-client-patient relationship.

Valid Veterinarian-Client-Patient Relationship (VCP or VCPR):
See Patient-Healthcare Professional Relationship
A valid VCPR exists when these conditions apply:
• The client (owner or owner’s agent of the animal[s]) has given the responsibility of medical care to the veterinarian and has agreed to follow the instructions of the veterinarian, and;
• the veterinarian has assumed the responsibility from the client for making clinical judgement regarding the health of the animal(s), the need for medical treatment, and for ensuring the provision of ongoing medical care for the animal(s);
• the veterinarian has sufficient knowledge of the health status of the animal(s) and the care received or to be received. The knowledge has been obtained through a recent examination of the animal(s) and the premises where they are (it is) kept or through a history of medically appropriate and timely examinations and interventions, and;
• the veterinarian is readily available, or has made the necessary arrangements with another veterinarian, for ongoing medical care of adverse reactions or therapy failure.

Withdrawal Period:
The length of time between the last administration of a drug to an animal and the time when tissues or products collected from the treated animal for consumption as food contain a level of residue of the drug that would not likely cause injury to human health. (Food and Drug Regulations C.01.001)
7.0 Associated Documents/Links

Guidelines for Bulk Compounding of Products in Hospitals, Canadian Society of Hospital Pharmacists, Ottawa, Ontario 1992.

Guidelines for Preparation of Sterile Products in Pharmacies, Canadian Society of Hospital Pharmacists, Ottawa, Ontario 1996.


Guidelines For The Legitimate Use Of Compounded Drugs in Veterinary Practice, Canadian Veterinary Medical Association, 2005

Guidelines to Pharmacy Compounding (Draft), National Association of Pharmacy Regulatory Authorities (NAPRA), Ottawa, Ontario 2005


USP Chapter <795> Pharmaceutical Compounding: Nonsterile Preparations

USP Chapter <797> Pharmaceutical Compounding: Sterile Preparations

Some of the following hyperlinks are to sites of organizations or other entities that are not subject to the Official Language Act. The material found there is therefore in the language(s) used by the sites in question

Website addresses:

College of Pharmacies
British Columbia: College of Pharmacists of British Columbia
Alberta: Alberta college of pharmacists
Saskatchewan: Saskatchewan College of Pharmacists
Manitoba: Manitoba Pharmaceutical Association
Ontario: Ontario College of Pharmacists
Quebec: Ordre des pharmaciens du Québec
New Brunswick: New Brunswick Pharmaceutical Society
Nova Scotia: Nova Scotia College of Pharmacists
Newfoundland: Newfoundland & Labrador Pharmacy Board
Prince Edward Island: Prince Edward Island Pharmacy Board
Yukon: Yukon Community Services
Northwest Territories: Northwest Territories Department of Health and Social Services

Health Canada
DIN Applications: Guideline on Preparation of DIN Submissions
Drug Establishment Licences: Drug Establishment Licences
Drug Submissions: Guidance on Drug Establishment Licences (GUIDE-0002)
EDR: Veterinary Drugs - Emergency Drug Release (EDR)
Good Manufacturing Practices: Good Manufacturing Practices - Guidance documents
HPFBI: Health Products and Food Branch Inspectorate - Compliance and Enforcement
SAP: Special Access to Drugs and Health Products

Associations
ASHP: American Society of Health-System Pharmacists
CSHP: Canadian Society of Hospitals Pharmacists
NAPRA: National Association of Pharmacy Regulatory Authorities

8.0 Authors
This Policy Framework was developed by the Health Products and Food Branch Inspectorate in collaboration with other Health Products and Food Branch directorates and members of the April 2004 focus group session.
## General Guideline on Compounding and Manufacturing Activities

<table>
<thead>
<tr>
<th>Compounding</th>
<th>Manufacturing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>1) Is there a demonstrated patient-healthcare professional relationship?</td>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>2) Is there third party reselling of the product outside of the patient-healthcare professional relationship?</td>
<td>No</td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>3) Is the activity regulated, and facility possibly inspected, by the province/territory?</td>
<td>Yes</td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>4) If producing product in anticipation of a prescription, is the amount produced consistent with the history of prescriptions received?</td>
<td>No</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>5) Is there an inordinate amount of product produced or on a regular basis?</td>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>6) Is an identical product (e.g. dosage form, strength, formulation) commercially available?</td>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>7) Is the product and/or compounding service promoted or advertised to the general public rather than strictly to healthcare professionals?</td>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>8) Does the drug product require only minor modification prior to direct administration when such modification amounts to mere directions for use?</td>
<td>Yes</td>
</tr>
</tbody>
</table>
PREFACE

This is the 1992 edition of the Canadian Society of Hospital Pharmacists (CSHP) Guidelines for Bulk Compounding of Products in Hospitals. It is one of a series of documents establishing criteria for the practice of pharmacy in hospitals.

These Guidelines were developed to assist hospital pharmacists to assess current practices in bulk compounding and to develop appropriate procedures and controls relative to bulk compounding.

Bulk compounding is an integral part of hospital pharmacy practice. (See CSHP Standards of Practice.) Often the institution's goals and scope of medical staff practices require pharmacy's participation in research as well as in the development of unique dosage forms. This capability in pharmacy facilitates optimum medical management of patients.

1. SCOPE

1.1 These Guidelines set forth procedures and controls to assist in assuring the quality of a bulk compound product.

1.2 These Guidelines are intended to include all non-sterile and sterile products prepared from raw materials. (Intravenous products prepared from commercially available injectable products are excluded.) Sterile injectable products should also comply with the Intravenous Therapy Guidelines. (See Bibliography #2)

1.3 These Guidelines were intended to augment but not replace the hospital's existing policies and procedures relative to bulk compounding.

2. DEFINITIONS

The following definitions apply in these Guidelines:

Bulk compounding - the preparation of products which are not commercially available in anticipation of a physician's order.

Commerciy available (product) - a pharmaceutical product authorized for use in Canada by the Health Protection Branch, Health and Welfare Canada, and having received Notice of Compliance, has been assigned a Drug Identification Number (DIN) and marketed in Canada.

Master Formula - a set of instructions outlining in detail the materials, equipment, and procedures required to produce a specific quantity of a product.

WHMIS (Workplace Hazardous Materials Information Systems) - federal and provincial legislation to ensure information regarding hazards of materials used in workplaces is provided to employers and employees.

3. PERSONNEL

All bulk compounding should be conducted under the supervision of a pharmacist who possesses the knowledge, experience and ability to assume the responsibility for same. All personnel handling materials affected by the WHMIS legislation should receive the proper training.

4. PREMISES

The area designated for bulk compounding should:

(a) be sanitary;
(b) permit effective cleaning of all surfaces;
(c) minimize the potential for contamination of the drug;
(d) minimize the potential for the addition of any extraneous material; and
(e) be conducive to the orderly flow of work.

5. EQUIPMENT

5.1 The equipment used in bulk compounding should:

(a) permit effective cleaning;
(b) minimize the potential for contamination of the product;
(c) minimize the potential for the addition of extraneous material to the product;
(d) be operated only for its intended use;
(e) be subject to preventative maintenance procedures; and
(f) be checked periodically for proper functioning and calibration.

5.2 Policies and procedures related to the use and maintenance of such equipment should be in accordance with the hospital's policies and procedures pertaining to occupational health and safety.

6. BULK COMPOUNDING CONTROL

6.1 Procedures

6.1.1 Written procedures should be in place for each bulk compounded product to ensure that the end product will meet the specifications for that product. A pharmacists shall assume responsibility for the final product and carry out appropriate checks at critical steps in the process.
6.1.2
The hygiene of all personnel participating in bulk compounding should be guided by policy and procedures within the department as well as the hospital employees' health and safety requirements.

6.1.3
Protective apparel may be appropriate to minimize contamination of the product during processing or packaging and to help protect the employee.

6.2 Master Formula
The master formula should indicate:
(a) the name of product;
(b) the dosage form of the product;
(c) the specifications and source of each raw material used;
(d) the formulation of each batch stating:
   (i) weights and measures of each raw material; and
   (ii) theoretical yield;
(e) the equipment required;
(f) a description of each step in the compounding process with special notations as required (e.g., which steps or measurements must be verified by a pharmacist or a second person);
(g) the shelf life, when applicable;
(h) the storage requirements;
(i) specific packaging requirements;
(j) a sample label, including WHMIS and auxiliary labelling where applicable;
(k) the quality control testing to be performed, when applicable; and
(l) reference sources for the formula, stability data, if available.

6.3 Production Records
6.3.1
A separate production record should be used for each batch compounded.

6.3.2
The production record should include:
(a) the date of compounding;
(b) the lot or batch number assigned to the compounded product;
(c) the manufacturer's name and lot number of each raw material used;
(d) a provision for sign-off of each step in the compound for the person compounding and the person checking;
(e) the process, including weights and measures performed;
(f) the results of all quality control testing;
(g) a statement of final yield;
(h) signatures for final verification and authorization for release;
(i) a sample label; and
(j) the expiry date of the product.

6.4 Raw Material
6.4.1
The quality and identity of all raw materials used in bulk compounding should be verified using a certificate of analysis from the chemical supplier or the label claims of commercially available products used in the compounding process.

6.4.2
Specifications should be of pharmacopoeial or equivalent status.

6.5 Labelling
The labelling of the finished product should be permanent and contain descriptive information including:
(a) the name of product;
(b) the strength of product;
(c) the dosage form of product;
(d) the lot or batch number;
(e) storage conditions, when applicable;
(g) the expiry date;
(h) auxiliary labels; and
(i) WHMIS labelling where applicable.

6.6 Packaging
The packaging of the finished product should:
(a) be appropriate for the dosage form;
(b) protect the product from light and moisture as necessary;
(c) minimize the potential for interaction between the drug and the container; and
(d) be sterile and free from particulate matter for sterile products.

6.7 Record Keeping
Records should be kept for an appropriate period of time in compliance with hospital procedures.

Note: The Good Manufacturing Practices for Drug Manufacturers and Importers, Health and Welfare, Canada, suggests a period of one year after the expiration date on the label of the compounded product.

6.8 Reporting
Hospitals should comply with all reporting regulations required by the Health Protection Branch.

6.9 Quality Control
6.9.1 Premises
Written procedures for cleaning the bulk compounding area should include:
(a) the cleaning interval;
(b) cleaning agents and their concentrations; and
(c) disposal of waste material and debris.
6.9.2 Equipment
Routine equipment maintenance, calibration, and certification should be defined, documented, and carried out.

6.9.3 End Product Testing

6.9.3.1 Non-sterile Products
Appropriate end product testing methods should be performed.

6.9.3.2 Sterile Products
Sterility tests should be performed on bulk compounded sterile products.

7. BIBLIOGRAPHY


4. WHMIS - see federal Bill - C-70 and provincial legislation on Occupational Health and Safety.
Repackaging: Guidelines for Healthcare Facilities

Published by the Canadian Society of Hospital Pharmacists (CSHP), Ottawa, Ontario. 1998 edition. Use of this document was approved by CSHP Council in 1998.

Suggested citation:


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Fax: 613.736.5660
Internet: www.cshp.ca

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All inquiries regarding this publication, including requests for interpretation, should be addressed to the Canadian Society of Hospital Pharmacists using the above contact information.
Repackaging: Guidelines for Healthcare Facilities

PREFACE

This is the 1998 edition of the Canadian Society of Hospital Pharmacists (CSHP) Repackaging: Guidelines for Healthcare Facilities. Pharmacy departments often have to repack drugs because the required quantities are not commercially available. These guidelines were developed to assist pharmacists working in health care facilities in assessing current repackaging practices and in developing appropriate procedures and controls for drug repackaging within their own facilities.

These guidelines were approved under the title of Guidelines for Repackaging Products in Health Care Facilities; the title was fine-tuned in 2009.

1. SCOPE

1.1

These guidelines establish minimum requirements for pharmacy departments which engage in the repackaging of drug products, and are intended to optimize the quality and safety of repackaged pharmaceuticals.

1.2

These guidelines are intended to augment but not to replace the department's existing policies and procedures relative to repackaging.

1.3

These guidelines are not intended to include intravenous admixtures prepared using commercially available injectable products. In preparing intravenous admixtures, the pharmacist should refer to the Sterile Preparation of Medicines: Guidelines for Pharmacies.

1.4

The pharmacist may also refer to the Pharmacy Technicians: Guidelines on the Delegation of Functions to Pharmacy Technicians.

2. GLOSSARY OF TERMS, ABBREVIATIONS, AND SYMBOLS

The definitions given below apply to the terms used in these guidelines. They may have different meanings in other contexts.

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commercially available (product)</td>
<td>A pharmaceutical product authorized for use in Canada by the Health Protection Branch, Health Canada, i.e. notice of compliance received, a Drug Identification Number (DIN) assigned, and marketed in Canada.</td>
</tr>
<tr>
<td>Pharmacy control number</td>
<td>A unique number assigned to each batch of repackaged product. This number can be used to trace back to the repackaging record, lot number, and original expiry date. Where computerized packaging equipment does not allow a unique number, the manufacturer's number can be used.</td>
</tr>
</tbody>
</table>

CSHP Mission:
CSHP is the national voice of pharmacists committed to the advancement of safe, effective medication use and patient care in hospitals and related healthcare settings.
3. PERSONNEL

All repackaging shall be conducted under the supervision of a pharmacist who possesses the knowledge, experience and ability deemed necessary by the director to assume the responsibility for same.

4. PREMISES

The area designated for repackaging shall:

a) be sanitary;
b) permit effective cleaning of all surfaces;
c) minimize the potential for contamination of the drug; and
d) be conducive to the orderly flow of work.

5. EQUIPMENT

The equipment used in repackaging shall:

a) permit the effective cleaning of its surfaces;
b) minimize the potential for contamination of the product;
c) be operated only for its intended use; and
d) be maintained under health care facility policies and procedures pertaining to health and safety.

6. REPACKAGING CONTROL

6.1 Procedures

Written procedures shall be in place for repackaging to ensure that the end product will meet the specifications for that product.

6.2 Repackaging Records

6.2.1

A separate repackaging record shall be kept for each batch repackaged. This may be manually produced or maintained in a computerized database.

6.2.2

The repackaging record shall include:

a) generic name of drug;
b) name of manufacturer;
c) dosage form;
d) strength;
e) pharmacy control number;
f) manufacturer's lot number;
g) date of repackaging;
h) number of units repackaged;
i) quantity in each unit repackaged;
j) expiry date of the original container;
k) expiry date of the repackaged container;
l) identification of the repackager and checker;
m) a sample of the label; and
n) a description of packaging materials and equipment used.

6.2.3

Records should be kept for an appropriate period of time.

Note: The Good Manufacturing Practice (GMP) Guidelines, Therapeutic Products Program, Health Canada, suggest a period of one year after the expiration date on the original manufacturer's label.

6.3 Pharmaceutical Product for Repackaging

6.3.1

The colour, odour, appearance and markings of the pharmaceutical product shall be inspected prior to use.

6.3.2

The manufacturer's container shall be examined for evidence of water damage, contamination or other deleterious effects.
Repackaging: Guidelines for Healthcare Facilities

6.3.3

The following characteristics of all packaging materials used shall be available:

a) composition;
b) light transmission;
c) size;
d) thickness;
e) moisture permeability;
f) sealing temperature; and

g) storage requirements.

Note: Latex-free packaging materials should be considered in accordance with individual health care facility guidelines and practices.

6.4 Packaging

6.4.1

The packaging of the finished product shall:

a) be appropriate for the dosage form;
b) protect the product from light and moisture as necessary; and
c) minimize the potential for interaction between the drug and the container.

Note: In the absence of accurate stability information, drugs supplied by the manufacturer in plastic should be repackaged in plastic, and those drugs supplied by the manufacturer in glass should be repackaged in glass.

6.4.2

Packaging material should be stored in accordance with the manufacturer’s instructions.

6.4.3

Pharmaceuticals shall not be repackaged more than once. This is due to the lack of stability, information and the need to track each repackaged dose.

6.5 Labelling

6.5.1

A lot numbering system shall be devised to facilitate the identification of each batch.

6.5.2

The label of the finished product shall be permanent and shall contain descriptive information including:

a) generic name of product;
b) identification of manufacturer, i.e., name or code;
c) strength of product;
d) dosage form of product (if abbreviations are used, they should be approved by health care facility);
e) amount;
f) pharmacy control number;
g) storage conditions, when applicable;
h) auxiliary labels;
i) expiry date; and
j) Expiration periods shall be derived using any or all of the following references:
   i) manufacturers’ recommendations;
   ii) pharmaceutical compendia;
   iii) professional literature; and/or
   iv) in-house stability and/or sterility studies.

6.6 Storing the Repackaged Product

All repackaged products shall be stored in a temperature and humidity controlled environment to minimize degradation by heat and moisture.

6.7 Reporting

Health care facilities shall comply with all Health Protection Branch reporting requirements.
Repackaging: Guidelines for Healthcare Facilities

6.8 Quality Control

6.8.1 Premises

Written procedures for cleaning the repackaging area shall include:

a) the cleaning interval;
b) cleaning agents and their concentrations; and
c) disposal of waste material and debris.

6.8.2 Equipment

Routine equipment maintenance, calibration, and certification shall be defined, documented, and carried out.

6.8.3 End Product Verification

6.8.3.1 Procedures for end product verification shall be established by the pharmacy department.

6.8.3.2 A final check of the end product shall be performed.

6.8.3.3 Appropriate training shall be provided for staff involved in the checking process.

6.8.3.4 Ultimate responsibility for all repackaging operations shall rest with the pharmacist.

Note: Many health care facilities use automated packaging machinery as well as bar code/scanning technology. These may facilitate packaging and inventory maintenance processes and can be incorporated while adhering to practice parameters.

7. BIBLIOGRAPHY


CSHP Guidelines for Preparation of Sterile Products in Pharmacies, Ottawa, Canada, 1996.

Note: In 2009 the title of this document was fine-tuned to Sterile Preparation of Medicines: Guidelines for Pharmacies.


Note: In 2009 the title of this document was fine-tuned to Pharmacy Technicians: Guidelines on the Delegation of Functions to Pharmacy Technicians.
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Drug Distribution: Statement on Unit-Dose & Intravenous Admixture

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All inquiries regarding this publication, including requests for interpretation, should be addressed to the Canadian Society of Hospital Pharmacists using the above contact information.
Drug Distribution: Statement on Unit-Dose & Intravenous Admixture

CSHP ENDORSES THE UNIT-DOSE/INTRAVENOUS (I.V.) ADMIXTURE SYSTEM AS THE DRUG DISTRIBUTION SYSTEM OF CHOICE IN ORGANIZED HEALTH CARE SETTINGS IN CANADA.

The Unit-Dose system is part of the hospital’s system of drug distribution in which medications are dispensed for a 24-hour period. Although they are referred to as separate systems, the Unit-Dose system of dispensing oral products and the I.V. Admixture system of dispensing parenteral products are based upon the same principle that all drugs are compounded and dispensed by Pharmacy in a patient-specific, individually labelled and ready-to-administer form.

Evidence gathered over the past 35 years clearly shows that the Unit-Dose/I.V. Admixture system has significant advantages over other systems including:

a) reduced incidence of medication errors;
b) decreased medication-related activities for Nursing;
c) efficient use of Pharmacy and Nursing personnel;
d) improved drug monitoring;
e) reduced drug inventories and enabled activity-based costing, i.e. patient-specific accounting of drug cost;
f) reduced wastage and pilferage, i.e. improved drug use control;
g) increased adaptability to computerized procedures, e.g., bar coding, automated packaging, ward-based point-of-use technology; and
h) improved job satisfaction for health care professionals.

The Unit-Dose/I.V. Admixture system of drug distribution is safer for the patient, more efficient and economical for the institution, and provides optimized use of human resources.

BIBLIOGRAPHY


Summerfield MR. Unit dose primer. Bethesda (MD): American Society of Hospital Pharmacists; 1983.


* A 48-72 hour supply of medication may be acceptable in long-term care facilities.


CSHP Mission:
CSHP is the national voice of pharmacists committed to the advancement of safe, effective medication use and patient care in hospitals and related healthcare settings.
FOREWORD

These Guidelines were developed with the efforts of many individuals through the work of the CSHP Task Force to Develop Guidelines for Sterile Product Compounding. The need for such Guidelines was identified by a number of pharmacy organizations. CSHP invited participation from a broad cross section of the profession in Canada. Many organizations provided input by appointment of corresponding members to the Task Force:

Alberta Pharmaceutical Association
New Brunswick Pharmaceutical Society
Canadian Pharmaceutical Association
Newfoundland Pharmaceutical Association
Nova Scotia Pharmaceutical Society
Health Protection Branch, Health Canada
Ontario College of Pharmacists
Manitoba Pharmaceutical Association
Saskatchewan Pharmaceutical Association

The [core] Task Force was based in Vancouver, British Columbia. Comments were also provided by individuals with an expressed interest in this issue. The input was considered by the Task Force with a number of drafts prepared and circulated. The revision process also requested feedback from CSHP Branch Delegates and general members. The Task Force submitted the Guidelines to the CSHP Standards Committee with the document then going to the CSHP Publications Advisory Committee for review. The final document from this process was subsequently approved by CSHP Council. This process is the same for all Standards, Statements and Guidelines produced by the Society.

These Guidelines form part of a comprehensive list of Standards, Statements and Guidelines developed by the CSHP to reflect appropriate standards of practice for pharmacists in hospitals and related health care settings.

The Guidelines for Sterile Product Compounding represent the first time such extensive collaboration has been utilized in producing pharmacy practice guidelines. CSHP would like to thank all those individuals and organizations who participated in this process.

PREFACE

This is the 1996 edition of the Canadian Society of Hospital Pharmacists (CSHP) Guidelines for the Preparation of Sterile Products in Pharmacies.

1. SCOPE

1.1 These guidelines are intended to be used in situations where pharmacies are involved in the preparation of sterile products dispensed directly to patients or to be administered to patients within the jurisdiction of that pharmacy (i.e., hospitals, community pharmacies, nursing homes, home health care and others). Such situations are often referred to as aseptic manipulation of already approved sterile pharmaceutical products. However, these guidelines are also applicable to batch-scale operations for the production of sterile products which are not commercially available.

1.2 Sterile products intended for distribution or sale outside the jurisdiction of the compounding pharmacy are subject to the full provisions of the Food and Drugs Act. Health care facilities lacking the proper equipment and/or expertise, particularly those in remote locations may contract with an outside licensed pharmacy centre for the provision of compounding services. Such services shall be restricted to patient specific written prescriptions. Note: Any pharmacy centre which promotes or advertises that it compouds specific drugs or drug classes is subject to the full provisions of the Food and Drugs Act.

1.3 These guidelines do not apply to manufacturers of sterile pharmaceuticals as defined in provincial or federal laws and regulations.

1.4 The practices outlined herein are considered general guides and they may be adapted to meet individual needs. The equivalence of alternate approaches should be validated. In exceptional situations, nothing precludes pharmacists from making risk-benefit decisions to prepare sterile products outside these guidelines (e.g., compassionate or immediate use [i.e., within one hour]).

1.5 These guidelines do not address issues relating to the protection of personnel preparing or handling hazardous pharmaceuticals such as caustic, cytotoxic or radiopharmaceuticals. Refer to CSHP Guidelines for the Handling and Disposal of Hazardous Pharmaceuticals.

2. DEFINITIONS

The definitions given below apply to the terms used in these Guidelines. They may have different meanings in other contexts.

Aseptic Preparation/Technique - the use of procedures in the preparation of sterile products which minimize or prevent the introduction of micro-organisms.

Batch Preparation - compounding or repackaging of multiple units, not for immediate use, in a single process, by the same operator in accordance with a standardized batch preparation procedure.

Critical Surface - surfaces which come in contact with sterilized product or packaging materials.
Packaging Material - those packaging components in direct contact with the sterile product.

Raw Material - any substance of defined quality used in the preparation of a sterile product, but excluding packaging materials.

Sterile - the absence of micro-organisms capable of reproducing themselves.

Sterile Product Preparation Areas (Refer to Appendix 1)
- Aseptic Preparation Area - a room or area designated for the preparation of sterile products. This area includes the critical area and may include a clean room.
- Clean Room - an aseptic preparation area with defined environmental control of particulate and microbial contamination (Grade C or D room), constructed and used in such a way as to reduce the introduction, generation and retention of contaminants.
- Critical Area - a grade A area intended to protect sterile products manufactured within the area from any secondary microbial contamination. The critical area within a pharmacy is usually the laminar airflow hood or biological safety cabinet located within the aseptic preparation area or clean room.

3. POLICIES AND PROCEDURES

3.1 General principles

3.1.1 There shall be up-to-date policies and procedures written and available for all persons involved in the preparation of sterile products.

3.1.2 Reviews, revisions and updates shall be done at least annually, or more frequently if necessary.

3.1.3 Policies and procedures shall be prepared and verified by qualified personnel.

3.2 Scope

3.2.1 The policies and procedures should cover the following areas:
(a) Personnel requirements:
   (i) verification of knowledge and credentials;
   (ii) orientation and training;
   (iii) responsibilities of all personnel involved in the preparation of sterile products;
   (iv) competency evaluation; and,
   (v) requirements for health and hygiene;
(b) Raw materials and packaging materials;
(c) Storage and handling:
   (i) supplies;
   (ii) components; and,
   (iii) end product;
(d) Facilities, equipment and sanitation:
   (i) use and maintenance of facilities and equipment; and,
   (ii) program for regular cleaning of facilities and equipment;
(e) Garb;
(f) Aseptic product preparation techniques:
   (i) specific procedures including disposal of supplies and components; and,
   (ii) development and maintenance of master worksheets including: formulae, component records, preparation procedures, labels, testing requirements;
(g) Labelling:
   (i) format and content;
   (ii) label handling;
   (iii) expiration date establishment; and,
(h) Process validation:
   (i) program for certification of equipment;
   (ii) program for certification of personnel; and,
   (iii) program for environmental monitoring;
(i) End product testing and release; and,
(j) Documentation.

4. PERSONNEL

4.1 Designated pharmacist

4.1.1 A pharmacist with sufficient training and/or experience shall be designated as responsible for sterile production operations.

4.1.2 The designated pharmacist shall be knowledgeable in the following areas:
(a) aseptic technique and contamination factors;
(b) environmental monitoring, facilities, equipment and supplies;
(c) parenteral routes of drug administration;
(d) methods and equipment for administration of drugs;
(e) procedures for the preparation, compounding, distribution and storage of sterile products;
(f) documentation, general quality control and assurance procedures;
(g) the chemical, pharmaceutical and clinical properties of all the ingredients in a sterile product;
(h) sterilization techniques and process validation;
(i) the principles of current Good Manufacturing Practices; and,
(j) the principles of microbiology.

4.2 Responsibilities of designated pharmacist

4.2.1 The designated pharmacist shall ensure that all sterile products have the identity, strength, quality and purity purported for the preparation.

4.2.2 The designated pharmacist should be responsible for the training and evaluation of all staff working in the area.
4.3 Training and evaluation

4.3.1 Persons preparing sterile preparations shall have received adequate orientation, suitable didactic and experiential training (e.g., videotapes, formal training programs) in aseptic techniques, proper gowning and gloving, and clean room procedures; have demonstrated competence through written or practical testing.

4.3.2 Regular ongoing training programs and evaluations should be available for all personnel to maintain expertise in sterile product preparation.

4.4 Hygiene

4.4.1 Personnel involved in sterile preparation should maintain high standards of personal hygiene and cleanliness.

4.4.2 Personnel with any health condition which may adversely affect the safety and quality of drug products shall be assessed and exempted from responsibilities in the area if necessary.

4.5 Untrained personnel

4.5.1 Untrained personnel shall not enter the aseptic preparation area unless they are supervised and informed of procedures to follow to maintain the aseptic environment.

5. RAW MATERIALS

5.1 General

5.1.1 If any raw materials are not finished sterile pharmaceuticals from a manufacturer, further testing may be required to determine the content of each lot of raw materials before it is used to make a sterile preparation.

5.2 Non-sterile, Non-compendial Grade Pharmaceuticals

5.2.1 Non-sterile raw materials which are not a compendial grade or better shall either be validated by a vendor’s Certificate of Analysis for identity, purity and potency of each lot, or be quarantined and assayed by a competent laboratory prior to being released by the designated pharmacist for the preparation of sterile products.

5.3 Non-sterile, Compendial Grade Pharmaceuticals

5.3.1 The labelled contents of raw materials may be accepted when the product is labelled as compendial grade or better and the product has been stored and handled appropriately.

6. STORAGE AND HANDLING

6.1 General

6.1.1 Every component of a sterile product and the finished product itself shall be stored and handled in such a way that its physical and chemical integrity is maintained.

6.2 Storage and handling of components

6.2.1 Drugs, equipment and containers used to prepare sterile products shall be stored under conditions which ensure cleanliness, prevent contamination and deterioration, and allow easy inspection and rotation.

6.2.2 Drugs, equipment and containers used in the preparation of sterile products shall be inspected before use for expiry date, contamination or damage to packaging. Expired, contaminated or damaged items shall not be used.

6.2.3 Drugs, equipment and containers shall be removed from their outer shipping cartons prior to their introduction into the aseptic preparation area.

6.2.4 Any procedures which generate or disseminate particles within the aseptic preparation area during processing shall be minimized or eliminated.

6.2.5 Containers chosen for sterile products shall be non-interactive with the product and of a suitable nature to protect the sterility and the physical and chemical integrity of the product.

6.3 Storage and handling of finished product

6.3.1 The finished product shall be stored under conditions which will protect its physical and chemical integrity until use.

7. FACILITIES, EQUIPMENT AND SANITATION (SEE APPENDIX 1)

7.1 Facilities

7.1.1 The aseptic preparation area shall be designed, operated and managed so as to minimize microbial and particulate contamination. The aseptic preparation area should be a limited-access area that is separated from other pharmacy operations.
7.1.2 The aseptic preparation area shall be clean, and should be of sufficient size and well lit. Premises should be designed and maintained in a manner which will prevent entry of insects and migration of extraneous material from outside.

7.1.3 Floors, walls or partitions and ceilings of the aseptic preparation area should be non-porous and washable so they can be cleaned regularly. All exposed surfaces should be smooth, impervious and unbroken to minimize the shedding or accumulation of particles or microorganisms and to permit the repeated applications of cleaning agents and disinfectants.

7.1.4 Sinks and drains should be avoided and should be excluded from aseptic preparation areas wherever possible. Where installed they should be designed, located and maintained so as to minimize risks of microbial or foreign material contamination generated during sink usage.

7.1.5 Access to the aseptic preparation area shall be limited. Individuals who are required to be in the area shall be properly attired.

7.1.6 Refrigeration facilities and freezing capabilities where applicable shall be available to store supplies and sterile products.

7.1.7 To help reduce the particle burden in the aseptic preparation area, an adjacent support area or anteroom is recommended. Appropriate activities for the adjacent support area include: handwashing, gowning/gloving, cleaning and disinfecting of containers and supplies. The adjacent support area should be clean, distinct and if possible, separated from the general pharmacy environment by a barrier (e.g., plastic curtains, partitions, walls).

7.1.8 When a room is designated as a clean room:
(a) it should be a Grade C or D clean room (Class 100,000 or better);
(b) it should have suitable ante-rooms and changing areas;
(c) it should have a sufficient airflow and a positive pressure differential relative to adjacent uncontrolled areas;
(d) it should contain the minimum of projecting ledges, shelves, cupboards and equipment, and no uncleanable recesses, to reduce accumulation of dust and to facilitate cleaning;
(e) operations in a clean room should be visible at all times to outside observers; and,
(f) observation and inspection should be conducted from outside the cleanroom where practicable.

7.1.9 Laminar airflow units shall be positioned so as not to create air turbulence for each other.

7.2 Equipment

7.2.1 Sterile products shall be prepared in a Grade A (Class 100) horizontal or vertical laminar airflow hood (critical area). The laminar airflow hood should be kept running continuously. If the hood is turned off, the hood should not be used for at least 30 minutes after being turned on, or as specified by the manufacturer. All critical laminar airflow hood surfaces shall be cleaned and disinfected after each hood start-up and daily before work begins. The work surface of the hood should be cleaned before each production sequence.

7.2.2 Large pieces of equipment, such as tanks, carts, tables, etc., used in the aseptic preparation area shall be made of material that is easily cleaned. Stainless steel is recommended.

7.2.3 The parts of production equipment that come into contact with the product shall not be reactive, additive or absorbent to such an extent that it will affect the quality of the product and thus present any hazard.

7.2.4 Equipment surfaces that come into direct contact with sterile preparations shall be properly sterilized before introduction into the critical area. This includes such items as tubing, filters, reservoirs and other processing equipment.

7.2.5 Equipment surfaces that do not come into direct contact with the sterile preparation shall be properly cleaned and disinfected before being placed in the critical area.

7.2.6 Balances and measuring equipment of an appropriate range and precision shall be available for production and control operations.

7.2.7 Equipment repairs should be done outside the aseptic preparation area, where possible. Where not possible, repairs should be followed by a thorough cleaning and sanitization of the premises and equipment.

7.3 Sanitation

7.3.1 Hard surfaces shall be disinfected and cleaned regularly in accordance with written procedures. For example:
(a) floors - daily;
(b) adjacent work surfaces (e.g., shelves, tables, stools, etc.) - weekly; and,
(c) ceilings, walls - monthly, or as required to maintain cleanliness.

7.3.2 Disinfectants and detergents should be selected and used to prevent microbial contamination. Diluted solutions should be
kept in previously cleaned containers. They should not be stored for long periods unless sterilized and chemical stability has been established. Partly emptied containers should not be topped up.

7.3.3 Cleaning materials (e.g., mops, sponges) should be designated for use in aseptic preparation areas. They should be made of materials that generate a low level of particles.

7.3.4 An appropriate method of disposing of waste, including needles, should be established which does not allow accumulation in the aseptic preparation area.

8. **GARB**

8.1 **General principles**

8.1.1 All special garments, personal hygiene and work processes should be designed to minimize contamination.

8.1.2 Special garments shall be clean and provided at each work session or at least once a day. Special garments should not be worn outside the required work zone.

8.1.3 Before entering the aseptic preparation areas personnel shall:
(a) remove wristwatches and jewelry;
(b) remove cosmetics which can shed particles; and,
(c) wash their hands and arms up to the elbows with an antimicrobial skin cleanser for an appropriate length of time.

8.2 **Aseptic preparation area garb**

8.2.1 All personnel should don the following garb before entering the aseptic preparation area and remove it only upon exiting the area:
(a) clean, low particle generating garments;
(b) closed coats/gowns with elastic cuff; and,
(c) head and facial hair covering.

8.3 **Critical area garb**

8.3.1 All personnel shall don the following garb before working in the critical area and remove it only upon exiting the area:
(a) all requirements for aseptic preparation area;
(b) clean, non-powdered gloves which shall be disinfected regularly during operations with 70% isopropyl alcohol. The gloves shall be changed with each session or when their integrity is compromised; and,
(c) face mask. Face mask is optional if working in a hood with a vertical glass barrier.

8.4 **Clean room garb**

8.4.1 All personnel should don the following garb before working in a clean room and remove it only upon exiting the area:
(a) all requirements for aseptic preparation area;
(b) all requirements for critical area including face mask; and,
(c) foot coverings.

9. **ASEPTIC PRODUCT PREPARATION**

9.1 **General principles**

9.1.1 No sterile product should be prepared unless its stability, compatibility, purpose and route of administration are judged appropriate by a designated pharmacist. Master worksheets should be followed and any deviations from procedure appropriately documented and approved by the designated pharmacist.

9.1.2 When procedures are developed, the number of manipulations required for the production of a sterile product shall be minimized.

9.1.3 The preparation of sterile product shall be carried out under aseptic conditions (i.e., in a class 100 horizontal or vertical laminar airflow hood - Grade A environment).

9.2 **Aseptic preparation area**

9.2.1 Unrelated activities and conversation in critical and aseptic preparation areas shall be kept to a minimum.

9.2.2 Eating, drinking, chewing or smoking, or the storage of food, drink, smoking materials or personal items in the production and storage areas should be prohibited. In general, any unhygienic practice within the aseptic preparation area or in any other area where the product might be adversely affected, should be forbidden.

9.3 **Operator preparation**

9.3.1 Personnel shall wash hands with a suitable antimicrobial skin cleanser for an appropriate length of time at the beginning of their work and also when re-entering the aseptic preparation area.

9.3.2 Personnel shall don appropriate garb.

9.3.3 Personnel shall repeat the preparation process if contamination occurs.
9.4 Aseptic technique

9.4.1 Ingredients and vehicles shall be checked for defects, expiration date and damage before use.

9.4.2 All materials essential for processing the product should be placed in the critical area (i.e., laminar airflow hood) prior to processing.

9.4.3 All non-sterile item surfaces shall be disinfected with alcohol or other suitable antimicrobial agent before being placed into the critical area.

9.4.4 Activities and materials shall be arranged in the laminar airflow hood so as not to interrupt the airflow between the HEPA filter, critical surfaces and areas where sterile components, raw materials or drug products are exposed.

9.4.5 All processing shall be done at least 15 cm inside the edge of the laminar airflow hood or within the limits specified by the manufacturer.

9.4.6 Only one operator should work in the laminar airflow hood at any one time.

9.4.7 Precautions to minimize contamination shall be taken:
(a) direct contact between the critical surfaces or the sterile product with any non-sterile product or surface shall be avoided;
(b) all non-sterile critical surfaces shall be disinfected by swabbing with alcohol before puncture; and,
(c) the duration of exposure of the disinfected critical surface before processing should be minimized.

9.4.8 Precautions to minimize particulate contamination shall be taken:
(a) ampoules shall be opened and contents aspirated using techniques that minimize particulate contamination. Solutions should be filtered unless contraindicated;
(b) reconstituted powders shall be mixed carefully to ensure complete dissolution of the drug; and,
(c) needle entry into vials with rubber stoppers shall be done in a way which minimizes creation of rubber core particulates.

9.5 Sterilization

9.5.1 When products are made from non-sterile ingredients, an appropriate sterilization technique shall be chosen which ensures that the physical and chemical integrity of the product is maintained.

9.5.2 Sterile filtration shall be carried out in a Grade A (laminar airflow hood) environment.

9.5.3 The time between the start of the preparation of a solution and its filtration should be as short as possible.

9.6 Checking

9.6.1 Inspection and control procedures should be conducted outside the clean room or critical area whenever feasible.

9.6.2 For preparation using automated compounding devices, the quantity of ingredients shall be verified visually or by weighing the final product.

9.6.3 A pharmacist or delegate shall check the identity and amount of the ingredients in the sterile product versus the original prescription or master worksheet before the product is released.

10. EXPIRATION DATING

10.1 General

10.1.1 Expiration periods shall be established for each type of sterile product.

10.1.2 Every sterile product shall be clearly labelled with an expiration time and/or date.

10.2 Determining expiration periods

10.2.1 Expiration periods shall be derived using any or all of the following references:
(a) manufacturers' recommendations;
(b) pharmaceutical compendia;
(c) professional literature; and,
(d) in-house stability and/or sterility studies.

10.2.2 Documentation to support the derivation of assigned expiration periods shall be available.

11. LABELLING

11.1 Label components

11.1.1 Sterile preparations shall be labelled with the following information:
12.2 Equipment

12.2.1 Laminar airflow hoods shall be recertified by a certified contractor at least once a year or when they are relocated, to ensure operational efficiency and effectiveness.

12.2.2 A method should be established to calibrate and when possible, certify the accuracy of automated compounding devices used in processing.

12.2.3 Temperature of refrigerators and freezers used to store sterile preparations should be monitored to ensure they meet compendial requirements and the results documented.

12.2.4 Sterilization by filtration requires integrity testing of the filter after use (and before, if not done by the manufacturer) in order to detect any filter leaks or perforations that may have occurred during filtration, i.e., forward flow, bubble point, pressure hold tests.

12.2.5 Any other equipment used to manufacture or store sterile preparations should be qualified regularly.

12.3 Aseptic technique

12.3.1 There should be a validation process performed on each individual performing aseptic technique. This should be developed by the designated pharmacist and conducted by the designated pharmacist or delegate during training and be repeated on a regular basis (at least yearly) and more often if problems arise.

12.3.2 The validation process should be applied to each individual and each class or type of aseptic procedure which they will be assigned to perform.

12.3.3 The process should verify that the personnel are using correct aseptic technique to prepare sterile products encountered in typical work assignments.

12.3.4 Depending on the procedure being performed, process validation may include direct observation, media fills, or microbiologic monitoring of work surfaces.

12.4 Environmental monitoring

12.4.1 A scientifically sound program of environmental monitoring should be established to ensure standards are maintained.
12.4.2
Maximum microbial and particulate limits should be established along with the corrective course of action if limits are exceeded.

12.4.3
Suggested environmental monitoring for particulates and microorganisms:
(a) air samples should be taken at several places within the aseptic preparation area;
(b) surfaces should be monitored by the use of surface contact plates, the swab rinse technique, or other appropriate methods; and;
(c) warning systems should alert personnel when air pressure or airflow falls below established limits in rooms designed with air pressure or airflow differentials.

12.5 Documentation of the process

12.5.1
Documentation of all validation tests, cleaning and maintenance procedures should be kept and reviewed on a regular basis.

12.5.2
Verified duplicates of the master worksheet should be used as the controlling document for each batch.

12.5.3
The worksheet should be used to document the following:
(a) ingredient(s) name and strength;
(b) ingredient(s) quantity;
(c) ingredient(s) lot number;
(d) ingredient(s) manufacturer or supplier;
(e) container specifications and lot numbers;
(f) preparation procedures;
(g) equipment used during preparation;
(h) comparison of actual to anticipated yield;
(i) date of preparation;
(j) end product lot number;
(k) end product expiration date;
(l) end product name or code (when applicable e.g., multiple ingredient products);)
(m) identity of all personnel involved in preparation and release;
(n) end product testing specifications and results;
(o) storage requirements; and,
(p) label sample.

12.5.4
These requirements may be recorded on separate documents but they should be easily retrievable.

13. END PRODUCT TESTING AND RELEASE

13.1 End product testing

13.1.1
Written specifications with acceptance criteria should be developed for testing all finished products.

13.1.2
When a product is made from sterile pharmaceutical using sterile equipment, closed vessel techniques and employing few manipulations AND:
(a) when it is preserved with an appropriate preservative; OR,
(b) when it is to be completely used within 28 hours; OR,
(c) when it is prepared using batch processing, which includes sterility testing as part of a program of process validation; THEN,

(a) the identity and strength of all ingredients shall be verified by in-process observation, syringe pull backs and direct observation of all ingredients (i.e., vial and ampoule counts); AND,
(b) the quality shall be verified by inspection of the final product for particulates, clarity, colour, solution volume, leaks and container integrity.

13.1.3
When a product is made from sterile pharmaceutical using sterile equipment, closed vessel techniques and employing few manipulations AND:
(a) when it is NOT completely used within 28 hours; or,
(b) when it is prepared using batch processing which does not include sterility testing as part of a program of process validation; THEN,

(a) the identity and strength of all ingredients shall be verified by in-process observation, syringe pull backs and direct observation of all ingredients (i.e., vial and ampoule counts); AND,
(b) the batch shall be quarantined and a representative sample of the product shall be subjected to sterility testing.

13.1.4
When a product is prepared from non-sterile ingredients or using non-sterile equipment or employing open vessel techniques, the product shall be quarantined and a representative sample of the product shall be subjected to sterility, pyrogenicity, identity and potency testing.

13.1.5
Statistically valid sampling and testing plans should be developed which include acceptance criteria and which ensure conformance of the entire batch to all specifications.

13.2 Product failure

13.2.1
Products which fail to meet all specifications shall be rejected and disposed of, or where appropriate, reprocessed according to established procedures.

13.2.2
Reprocessed material shall meet all established specifications during final product testing.
13.3 Quarantine and release

13.3.1 Final products undergoing verification procedures or end product testing shall be quarantined until satisfactory completion of testing. The designated pharmacist or delegate shall authorize release.

14. DOCUMENTATION

14.1 General

14.1.1 Documentation is an essential part of the quality assurance system. Clearly written documentation prevents errors from verbal communication and permits tracing of individual prescription or batch history.

14.1.2 Specifications, master formulae, worksheets, procedures, and records shall be free from errors and available in writing.

14.2 Records

14.2.1 Records should be maintained for an adequate period of time for the following:
(a) personnel matters including training and certification:
(b) individual prescriptions and documentation as per provincial regulations;
(c) appropriately authorized and dated worksheets for batched products;
(d) complete data derived from all tests necessary to assure compliance with established specifications and standards, including process verification procedures and end product testing;
(e) equipment assembly, calibration and certification;
(f) maintenance, cleaning, sanitation and environmental monitoring; and,
(g) complaints, recalls and returns.

14.3 Storage of records

14.3.1 It is recommended that these documents be readily retrievable for a period of one year following the expiration date of the final preparation or longer, if required by provincial or federal law.

15. BIBLIOGRAPHY


10. CSHP Guidelines for the Handling and Disposal of Hazardous Pharmaceuticals (including Cytotoxic Drugs)
## APPENDIX 1

### BASIC ENVIRONMENTAL STANDARDS FOR THE MANUFACTURING OF STERILE PRODUCTS

<table>
<thead>
<tr>
<th>GRADE</th>
<th>U.S. FED STD 209D</th>
<th>AIR CHANGES PER HOUR</th>
<th>MAX. PERMITTED NO. OF PARTICLES PER m³ EQUAL TO OR ABOVE</th>
<th>MAX. PERMITTED NO. OF Viable MICROORGANISMS PER m³</th>
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</thead>
<tbody>
<tr>
<td>A laminar air flow work station</td>
<td>100</td>
<td>flow of 0.3 m/s (vertical) or 0.45 m/s (horizontal)</td>
<td>0.5 µm</td>
<td>5 µm</td>
</tr>
<tr>
<td>B</td>
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<td>5-20</td>
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<td>0</td>
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<td>100,000</td>
<td>5-20</td>
<td>3,500,000</td>
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</table>
Hazardous Pharmaceuticals (Including Cytotoxic Drugs): Guidelines for Handling and Disposal (1997)
Hazardous Pharmaceuticals (Including Cytotoxic Drugs): Guidelines for Handling and Disposal

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GUIDELINES FOR PREPARATION OF
STERILE PRODUCTS IN PHARMACIES

FOREWORD

These Guidelines were developed with the efforts of many individuals through the work of the CSHP Task Force to Develop Guidelines for Sterile Product Compounding. The need for such Guidelines was identified by a number of pharmacy organizations. CSHP invited participation from a broad cross-section of the profession in Canada. Many organizations provided input by appointment of corresponding members to the Task Force:

Alberta Pharmaceutical Association
New Brunswick Pharmaceutical Society
Canadian Pharmaceutical Association
Nova Scotia Pharmaceutical Society
Health Protection Branch, Health Canada
Ontario College of Pharmacists
Manitoba Pharmaceutical Association
Saskatchewan Pharmaceutical Association
Newfoundland Pharmaceutical Association

The (core) Task Force was based in Vancouver, British Columbia. Comments were also provided by individuals with an expressed interest in this issue. The input was considered by the Task Force with a number of drafts prepared and circulated. The revision process also requested feedback from CSHP Branch Delegates and general members. The Task Force submitted the Guidelines to the CSHP Standards Committee, with the document then going to the CSHP Publications Advisory Committee for review. The final document from this process was subsequently approved by CSHP Council. This process is the same for all Standards, Statements, and Guidelines produced by the Society.

These Guidelines form part of a comprehensive list of Standards, Statements, and Guidelines developed by the CSHP to reflect appropriate standards of practice for pharmacists in hospitals and related health care settings.

The Guidelines for Sterile Product Compounding represent the first time such extensive collaboration has been utilized in producing pharmacy practice guidelines. CSHP would like to thank all those individuals and organizations who participated in this process.

PREFACE

This is the 1996 edition of the Canadian Society of Hospital Pharmacists (CSHP) Guidelines for the Preparation of Sterile Products in Pharmacies.

1. SCOPE

1.1 These guidelines are intended to be used in situations where pharmacies are involved in the preparation of sterile products dispensed directly to patients or to be administered to patients within the jurisdiction of that pharmacy (i.e., hospitals, community pharmacies, nursing homes, home health care and others). Such situations are often referred to as aseptic manipulation of already approved sterile pharmaceutical products. However, these guidelines are also applicable to batch scale operations for the production of sterile products which are not commercially available.

1.2 Sterile products intended for distribution or sale outside the jurisdiction of the compounding pharmacy are subject to the full provisions of the Food and Drugs Act. Health care facilities lacking the proper equipment and/or expertise, particularly those in remote locations may contract with an outside licensed pharmacy centre for the provision of compounding services. Such services shall be restricted to patient specific written prescriptions.

Note: Any pharmacy centre which promotes or advertises that it compounds specific drugs or drug classes is subject to the full provisions of the Food and Drugs Act.

1.3 These guidelines do not apply to manufacturers of sterile pharmaceuticals as defined in provincial or federal laws and regulations.

1.4 The practices outlined herein are considered general guides and they may be adapted to meet individual needs. The equivalence of alternate approaches should be validated. In exceptional situations, nothing precludes pharmacists from making risk-benefit decisions to prepare sterile products outside these guidelines (e.g., compassionate or immediate use [i.e., within one hour]).

1.5 These guidelines do not address issues relating to the protection of personnel preparing or handling hazardous pharmaceuticals such as caustic, cytotoxic or radiopharmaceuticals. Refer to CSHP Guidelines for the Handling and Disposal of Hazardous Pharmaceuticals.

2. DEFINITIONS

The definitions given below apply to the terms used in these Guidelines. They may have different meanings in other contexts.

Aseptic Preparation/Technique - the use of procedures in the preparation of sterile products which minimize or prevent the introduction of micro-organisms.

Batch Preparation - compounding or repackaging of multiple units, not for immediate use, in a single process, by the same operator in accordance with a standardized batch preparation procedure.

Critical Surface - surfaces which come in contact with sterilized product or packaging materials.
Packaging Material - those packaging components in direct contact with the sterile product.

Raw Material - any substance of defined quality used in the preparation of a sterile product, but excluding packaging materials.

Sterile - the absence of microorganisms capable of reproducing themselves.

Sterile Product Preparation Areas (Refer to Appendix 1)
- Aseptic Preparation Area - a room or area designated for the preparation of sterile products. This area includes the critical area and may include a clean room.
- Clean Room - an aseptic preparation area with defined environmental control of particulate and microbial contamination (Grade C or D room), constructed and used in such a way as to reduce the introduction, generation and retention of contaminants.
- Critical Area - a grade A area intended to protect sterile products manufactured within the area from any secondary microbial contamination. The critical area within a pharmacy is usually the laminar airflow hood or biological safety cabinet located within the aseptic preparation area or clean room.

3. POLICIES AND PROCEDURES

3.1 General principles

3.1.1 There shall be up-to-date policies and procedures written and available for all persons involved in the preparation of sterile products.

3.1.2 Reviews, revisions and updates shall be done at least annually, or more frequently if necessary.

3.1.3 Policies and procedures shall be prepared and verified by qualified personnel.

3.2 Scope

3.2.1 The policies and procedures should cover the following areas:
(a) Personnel requirements:
   (i) verification of knowledge and credentials;
   (ii) orientation and training;
   (iii) responsibilities of all personnel involved in the preparation of sterile products;
   (iv) competency evaluation; and,
   (v) requirements for health and hygiene;
(b) Raw materials and packaging materials;
(c) Storage and handling:
   (i) supplies;
   (ii) components; and,
   (iii) end product;
(d) Facilities, equipment and sanitation:
   (i) use and maintenance of facilities and equipment; and,
   (ii) program for regular cleaning of facilities and equipment;
(e) Carb;
(f) Aseptic product preparation techniques:
   (i) specific procedures including disposal of supplies and components; and,
   (ii) development and maintenance of master worksheets including: formulae, component records, preparation procedures, labels, testing requirements;
(g) Labelling:
   (i) format and content;
   (ii) label handling;
   (iii) expiration date establishent; and,
(h) Process validation:
   (i) program for certification of equipment;
   (ii) program for certification of personnel; and,
   (iii) program for environmental monitoring;
(i) End product testing and release; and,
(j) Documentation.

4. PERSONNEL

4.1 Designated pharmacist

4.1.1 A pharmacist with sufficient training and/or experience shall be designated as responsible for sterile production operations.

4.1.2 The designated pharmacist shall be knowledgeable in the following areas:
(a) aseptic technique and contamination factors;
(b) environmental monitoring, facilities, equipment and supplies;
(c) parenteral routes of drug administration;
(d) methods and equipment for administration of drugs;
(e) procedures for the preparation, compounding, distribution and storage of sterile products;
(f) documentation, general quality control and assurance procedures;
(g) the chemical, pharmaceutical and clinical properties of all the ingredients in a sterile product;
(h) sterilization techniques and process validation;
(i) the principles of current Good Manufacturing Practices; and,
(j) the principles of microbiology.

4.2 Responsibilities of designated pharmacist

4.2.1 The designated pharmacist shall ensure that all sterile products have the identity, strength, quality and purity purported for the preparation.

4.2.2 The designated pharmacist should be responsible for the training and evaluation of all staff working in the area.
4.3 Training and evaluation

4.3.1 Persons preparing sterile preparations shall have received adequate orientation, suitable didactic and experiential training (e.g. videotapes, formal training programs) in aseptic techniques, proper gowning and gloving, and clean room procedures, have demonstrated competence through written or practical testing.

4.3.2 Regular ongoing training programs and evaluations should be available for all personnel to maintain expertise in sterile product preparation.

4.4 Hygiene

4.4.1 Personnel involved in sterile preparation should maintain high standards of personal hygiene and cleanliness.

4.4.2 Personnel with any health condition which may adversely affect the safety and quality of drug products shall be assessed and exempted from responsibilities in the area if necessary.

4.5 Untrained personnel

4.5.1 Untrained personnel shall not enter the aseptic preparation area unless they are supervised and informed of procedures to follow to maintain the aseptic environment.

5. RAW MATERIALS

5.1 General

5.1.1 If any raw materials are not finished sterile pharmaceuticals from a manufacturer, further testing may be required to determine the content of each lot of raw materials before it is used to make a sterile preparation.

5.2 Non-sterile, Non-compendial Grade Pharmaceuticals

5.2.1 Non-sterile raw materials which are not a compendial grade or better shall either be validated by a vendor's Certificate of Analysis for identity, purity, and potency of each lot, or be quarantined and assayed by a competent laboratory prior to being released by the designated pharmacist for the preparation of sterile products.

5.3 Non-sterile, Compendial Grade Pharmaceuticals

5.3.1 The labelled contents of raw materials may be accepted when the product is labelled as compendial grade or better and the product has been stored and handled appropriately.

6. STORAGE AND HANDLING

6.1 General

6.1.1 Every component of a sterile product and the finished product itself shall be stored and handled in such a way that its physical and chemical integrity is maintained.

6.2 Storage and handling of components

6.2.1 Drugs, equipment and containers used to prepare sterile products shall be stored under conditions which ensure cleanliness, prevent contamination and deterioration, and allow easy inspection and rotation.

6.2.2 Drugs, equipment and containers used in the preparation of sterile products shall be inspected before use for expiry date, contamination or damage to packaging. Expired, contaminated or damaged items shall not be used.

6.2.3 Drugs, equipment and containers shall be removed from their outer shipping cartons prior to their introduction into the aseptic preparation area.

6.2.4 Any procedures which generate or disseminate particles within the aseptic preparation area during processing shall be minimized or eliminated.

6.2.5 Containers chosen for sterile products shall be non-reactive with the product and of a suitable nature to protect the sterility and the physical and chemical integrity of the product.

6.3 Storage and handling of finished product

6.3.1 The finished product shall be stored under conditions which will protect its physical and chemical integrity until use.

7. FACILITIES, EQUIPMENT AND SANITATION (SEE APPENDIX 1)

7.1 Facilities

7.1.1 The aseptic preparation area shall be designed, operated and managed so as to minimize microbial and particulate contamination. The aseptic preparation area should be a limited-access area that is separated from other pharmacy operations.
7.1.2
The aseptic preparation area shall be clean, and should be of sufficient size and well lit. Premises should be designed and maintained in a manner which will prevent entry of insects and migration of extraneous material from outside.

7.1.3
Floors, walls or partitions and ceilings of the aseptic preparation area should be non-porous and washable so they can be cleaned regularly. All exposed surfaces should be smooth, impervious and unbroken to minimize the shedding or accumulation of particles or microorganisms and to permit the repeated applications of cleaning agents and disinfectants.

7.1.4
Sinks and drains should be avoided and should be excluded from aseptic preparation areas wherever possible. Where installed they should be designed, located and maintained so as to minimize risks of microbial or foreign material contamination generated during sink usage.

7.1.5
Access to the aseptic preparation area shall be limited. Individuals who are required to be in the area shall be properly attired.

7.1.6
Refrigeration facilities and freezing capabilities where applicable shall be available to store supplies and sterile products.

7.1.7
To help reduce the particle burden in the aseptic preparation area, an adjacent support area or anteroom is recommended. Appropriate activities for the adjacent support area include: handwashing, gowning/gloving, cleaning and disinfecting of containers and supplies. The adjacent support area should be clean, distinct and if possible, separated from the general pharmacy environment by a barrier (e.g., plastic curtains, partitions, walls).

7.1.8
When a room is designated as a clean room:
(a) it should be a Grade C or D clean room (Class 100,000 or better);
(b) it should have suitable anterooms and changing areas;
(c) it should have a sufficient airflow and a positive pressure differential relative to adjacent uncontrolled areas;
(d) it should contain the minimum of projecting ledges, shelves, cupboards and equipment, and no uncleanable recesses, to reduce accumulation of dust and to facilitate cleaning;
(e) operations in a clean room should be visible at all times to outside observers, and;
(f) observation and inspection should be conducted from outside the cleanroom where practicable.

7.1.9
Laminar airflow units shall be positioned so as not to create air turbulence for each other.

7.2 Equipment

7.2.1
Sterile products shall be prepared in a Grade A (Class 100) horizontal or vertical laminar airflow hood (critical area). The laminar airflow hood should be kept running continuously. If the hood is turned off, the hood should not be used for at least 30 minutes after being turned on, or as specified by the manufacturer. All critical laminar airflow hood surfaces shall be cleaned and disinfected after each hood start-up and daily before work begins. The work surface of the hood should be cleaned before each production sequence.

7.2.2
Large pieces of equipment, such as tanks, carts, tables, etc., used in the aseptic preparation area shall be made of material that is easily cleaned. Stainless steel is recommended.

7.2.3
The parts of production equipment that come into contact with the product shall not be reactive, additive or absorptive to such an extent that it will affect the quality of the product and thus present any hazard.

7.2.4
Equipment surfaces that come into direct contact with sterile preparations shall be properly sterilized before introduction into the critical area. This includes such items as tubing, filters, reservoirs and other processing equipment.

7.2.5
Equipment surfaces that do not come into direct contact with the sterile preparation shall be properly cleaned and disinfected before being placed in the critical area.

7.2.6
Balances and measuring equipment of an appropriate range and precision shall be available for production and control operations.

7.2.7
Equipment repairs should be done outside the aseptic preparation area, where possible. Where not possible, repairs should be followed by a thorough cleaning and sanitization of the premises and equipment.

7.3 Sanitation

7.3.1
Hard surfaces shall be disinfected and cleaned regularly in accordance with written procedures. For example:
(a) floors - daily;
(b) adjacent work surfaces (e.g., shelves, tables, stools, etc.) - weekly; and,
(c) ceilings, walls - monthly, or as required to maintain cleanliness.

7.3.2
Disinfectants and detergents should be selected and used to prevent microbial contamination. Diluted solutions should be
kept in previously cleaned containers. They should not be stored for long periods unless sterilized and chemical stability has been established. Partially emptied containers should not be topped up.

7.3.3 Cleaning materials (e.g., mops, sponges) should be designated for use in aseptic preparation areas. They should be made of materials that generate a low level of particles.

7.3.4 An appropriate method of disposing of waste, including needles, should be established which does not allow accumulation in the aseptic preparation area.

8. GARB

8.1 General principles

8.1.1 All special garments, personal hygiene and work processes should be designed to minimize contamination.

8.1.2 Special garments shall be clean and provided at each work session or at least once a day. Special garments should not be worn outside the required work zone.

8.1.3 Before entering the aseptic preparation areas personnel shall:
1. remove wristwatches and jewelry;
2. remove cosmetics which can shed particles; and,
3. wash their hands and arms up to the elbows with an antimicrobial skin cleanser for an appropriate length of time.

8.2 Aseptic preparation area garb

8.2.1 All personnel should don the following garb before entering the aseptic preparation area and remove it only upon exiting the area:
(a) clean, low particle generating garments;
(b) closed coats/gowns with elastic cuff; and,
(c) head and facial hair covering.

8.3 Critical area garb

8.3.1 All personnel should don the following garb before working in the critical area and remove it only upon exiting the area:
(a) all requirements for aseptic preparation area;
(b) clean, non-powdered gloves which shall be disinfected regularly during operations with 70% isopropyl alcohol. The gloves shall be changed with each session or when their integrity is compromised; and,
(c) face mask. Face mask is optional if working in a hood with a vertical glass barrier.

8.4 Clean room garb

8.4.1 All personnel should don the following garb before working in a clean room and remove it only upon exiting the area:
(a) all requirements for aseptic preparation area;
(b) all requirements for critical area including face mask; and,
(c) foot coverings.

9. ASEPTIC PRODUCT PREPARATION

9.1 General principles

9.1.1 No sterile product should be prepared unless its stability, compatibility, purpose and route of administration are judged appropriate by a designated pharmacist. Master worksheets should be followed and any deviations from procedure appropriately documented and approved by the designated pharmacist.

9.1.2 When procedures are developed, the number of manipulations required for the production of a sterile product shall be minimized.

9.1.3 The preparation of sterile product shall be carried out under aseptic conditions (i.e., in a class 100 horizontal or vertical laminar airflow hood - Grade A environment).

9.2 Aseptic preparation area

9.2.1 Unrelated activities and conversation in critical and aseptic preparation areas shall be kept to a minimum.

9.2.2 Eating, drinking, chewing or smoking, or the storage of food, drink, smoking materials or personal items in the production and storage areas should be prohibited. In general, any unhygienic practice within the aseptic preparation area or in any other area where the product might be adversely affected, should be forbidden.

9.3 Operator preparation

9.3.1 Personnel shall wash hands with a suitable antimicrobial skin cleanser for an appropriate length of time at the beginning of their work and also when re-entering the aseptic preparation area.

9.3.2 Personnel shall don appropriate garb.

9.3.3 Personnel shall repeat the preparation process if contamination occurs.
9.4 Aseptic technique

9.4.1 Ingredients and vehicles shall be checked for defects, expiration date and damage before use.

9.4.2 All materials essential for processing the product should be placed in the critical area (i.e., laminar airflow hood) prior to processing.

9.4.3 All non-sterile item surfaces shall be disinfected with alcohol or other suitable antimicrobial agent before being placed into the critical area.

9.4.4 Activities and materials shall be arranged in the laminar airflow hood so as not to interrupt the airflow between the HEPA filter, critical surfaces and areas where sterile components, raw materials or drug products are exposed.

9.4.5 All processing shall be done at least 15 cm inside the edge of the laminar airflow hood or within the limits specified by the manufacturer.

9.4.6 Only one operator should work in the laminar airflow hood at any one time.

9.4.7 Precautions to minimize contamination shall be taken:
(a) direct contact between the critical surfaces or the sterile product with any non-sterile product or surface shall be avoided;
(b) all non-sterile critical surfaces shall be disinfected by swabbing with alcohol before puncture; and,
(c) the duration of exposure of the disinfected critical surface before processing should be minimized.

9.4.8 Precautions to minimize particulate contamination shall be taken:
(a) ampoules shall be opened and contents aspirated using techniques that minimize particulate contamination. Solutions should be filtered unless contraindicated;
(b) reconstituted powders shall be mixed carefully to ensure complete dissolution of the drug; and,
(c) needle entry into vials with rubber stoppers shall be done in a way which minimizes creation of rubber core particulates.

9.5 Sterilization

9.5.1 When products are made from non-sterile ingredients, an appropriate sterilization technique shall be chosen which ensures that the physical and chemical integrity of the product is maintained.

9.5.2 Sterile filtration shall be carried out in a Grade A (laminar airflow hood) environment.

9.5.3 The time between the start of the preparation of a solution and its filtration should be as short as possible.

9.6 Checking

9.6.1 Inspection and control procedures should be conducted outside the clean room or critical area whenever feasible.

9.6.2 For preparation using automated compounding devices, the quantity of ingredients shall be verified visually or by weighing the final product.

9.6.3 A pharmacist or delegate shall check the identity and amount of the ingredients in the sterile product versus the original prescription or master worksheet before the product is released.

10. EXPIRATION DATING

10.1 General

10.1.1 Expiration periods shall be established for each type of sterile product.

10.1.2 Every sterile product shall be clearly labelled with an expiration time and/or date.

10.2 Determining expiration periods

10.2.1 Expiration periods shall be derived using any or all of the following references:
(a) manufacturers' recommendations;
(b) pharmaceutical compendia;
(c) professional literature; and,
(d) in-house stability and/or sterility studies.

10.2.2 Documentation to support the derivation of assigned expiration periods shall be available.

11. LABELLING

11.1 Label components

11.1.1 Sterile preparations shall be labelled with the following information:
12.2 Equipment

12.2.1
Laminar airflow hoods shall be recertified by a certified contractor at least once a year or when they are relocated. To ensure operational efficiency and effectiveness.

12.2.2
A method should be established to calibrate and when possible, certify the accuracy of automated compounding devices used in processing.

12.2.3
Temperature of refrigerators and freezers used to store sterile preparations should be monitored to ensure they meet compendial requirements and the results documented.

12.2.4
Sterilization by filtration requires integrity testing of the filter after use (and before, if not done by the manufacturer) in order to detect any filter leaks or perforations that may have occurred during filtration, i.e., forward flow, bubble point, pressure hold tests.

12.2.5
Any other equipment used to manufacture or store sterile preparations should be qualified regularly.

12.3 Aseptic technique

12.3.1
There should be a validation process performed on each individual performing aseptic technique. This should be developed by the designated pharmacist and conducted by the designated pharmacist or delegate during training and be repeated on a regular basis (at least yearly) and more often if problems arise.

12.3.2
The validation process should be applied to each individual and each class or type of aseptic procedure which they will be assigned to perform.

12.3.3
The process should verify that the personnel are using correct aseptic technique to prepare sterile products encountered in typical work assignments.

12.3.4
Depending on the procedure being performed, process validation may include direct observation, media fills, or microbiologic monitoring of work surfaces.

12.4 Environmental monitoring

12.4.1
A scientifically sound program of environmental monitoring should be established to ensure standards are maintained.
12.4.2 Maximum microbial and particulate limits should be established along with the corrective course of action if limits are exceeded.

12.4.3 Suggested environmental monitoring for particulates and microorganisms:
   (a) air samples should be taken at several places within the aseptic preparation area;
   (b) surfaces should be monitored by the use of surface contact plates, the swab rinse technique, or other appropriate methods; and,
   (c) warning systems should alert personnel when air pressure or airflow falls below established limits in rooms designed with air pressure or airflow differentials.

12.5 Documentation of the process

12.5.1 Documentation of all validation tests, cleaning and maintenance procedures should be kept and reviewed on a regular basis.

12.5.2 Verified duplicates of the master worksheet should be used as the controlling document for each batch.

12.5.3 The worksheet should be used to document the following:
   (a) ingredient(s) name and strength;
   (b) ingredient(s) quantity;
   (c) ingredient(s) lot number;
   (d) ingredient(s) manufacturer or supplier;
   (e) container specifications and lot numbers;
   (f) preparation procedures;
   (g) equipment used during preparation;
   (h) comparison of actual to anticipated yield;
   (i) date of preparation;
   (j) end product lot number;
   (k) end product expiration date;
   (l) end product name or code (when applicable [e.g., multiple ingredient products]);
   (m) identity of all personnel involved in preparation and release;
   (n) end product testing specifications and results;
   (o) storage requirements; and,
   (p) label sample.

12.5.4 These requirements may be recorded on separate documents but should be easily retrievable.

13. END PRODUCT TESTING AND RELEASE

13.1 End product testing

13.1.1 Written specifications with acceptance criteria should be developed for testing all finished products.

13.1.2 When a product is made from sterile pharmaceutical using sterile equipment, closed vessel techniques and employing few manipulations AND:
   (a) when it is preserved with an appropriate preservative OR.
   (b) when it is to be completely used within 28 hours OR.
   (c) when it is prepared using batch processing, which includes sterility testing as part of a program of process validation; THEN,
   (a) the identity and strength of all ingredients shall be verified by in-process observation, syringe pull backs and direct observation of all ingredients (i.e., vial and ampoule counts);
   AND,
   (b) the quality shall be verified by inspection of the final product for particulates, clarity, colour, solution volume, leaks and container integrity.

13.1.3 When a product is made from sterile pharmaceutical using sterile equipment, closed vessel techniques and employing few manipulations AND:
   (a) when it is NOT completely used within 28 hours or.
   (b) when it is prepared using batch processing which does not include sterility testing as part of a program of process validation; THEN,
   (a) the identity and strength of all ingredients shall be verified by in-process observation, syringe pull backs and direct observation of all ingredients (i.e., vial and ampoule counts);
   AND,
   (b) the batch shall be quarantined and a representative sample of the product shall be subjected to sterility testing.

13.1.4 When a product is prepared from non-sterile ingredients or using non-sterile equipment or employing open vessel techniques, the product shall be quarantined and a representative sample of the product shall be subjected to sterility, pyrogenicity, identity and potency testing.

13.1.5 Statistically valid sampling and testing plans should be developed which include acceptance criteria and which ensure conformance of the entire batch to all specifications.

13.2 Product failure

13.2.1 Products which fail to meet all specifications shall be rejected and disposed of, or where appropriate, reprocessed according to established procedures.

13.2.2 Reprocessed material shall meet all established specifications during final product testing.
13.3 Quarantine and release

13.3.1 Final products undergoing verification procedures or end product testing shall be quarantined until satisfactory completion of testing. The designated pharmacist or delegate shall authorize release.

14. DOCUMENTATION

14.1 General

14.1.1 Documentation is an essential part of the quality assurance system. Clearly written documentation prevents errors from verbal communication and permits tracing of individual prescription or batch history.

14.1.2 Specifications, master formulae, worksheets, procedures, and records shall be free from errors and available in writing.

14.2 Records

14.2.1 Records should be maintained for an adequate period of time for the following:

(a) personnel matters including training and certification;
(b) individual prescriptions and documentation as per provincial regulations;
(c) appropriately authorized and dated worksheets for batched products;
(d) complete data derived from all tests necessary to assure compliance with established specifications and standards, including process verification procedures and end product testing;
(e) equipment assembly, calibration and certification;
(f) maintenance, cleaning, sanitation and environmental monitoring; and,
(g) complaints, recalls and returns.

14.3 Storage of records

14.3.1 It is recommended that these documents be readily retrievable for a period of one year following the expiration date of the final preparation or longer, if required by provincial or federal law.

15. BIBLIOGRAPHY


10. CSHP Guidelines for the Handling and Disposal of Hazardous Pharmaceuticals (including Cytotoxic Drugs)
APPENDIX 1

BASIC ENVIRONMENTAL STANDARDS FOR THE MANUFACTURING OF STERILE PRODUCTS

<table>
<thead>
<tr>
<th>GRADE</th>
<th>U.S. FED STD 209D</th>
<th>AIR CHANGES PER HOUR</th>
<th>MAX. PERMITTED NO. OF PARTICLES PER m³ EQUAL TO OR ABOVE</th>
<th>MAX. PERMITTED NO. OF Viable MICROORGANISMS PER m³</th>
</tr>
</thead>
<tbody>
<tr>
<td>A laminar air flow work station</td>
<td>100</td>
<td>flow of 0.3 m/s (vertical) or 0.45 m/s (horizontal)</td>
<td>0.5 um 3,500</td>
<td>5 um 0</td>
</tr>
<tr>
<td>B</td>
<td>100</td>
<td>5-20</td>
<td>3,500</td>
<td>0</td>
</tr>
<tr>
<td>C</td>
<td>10,000</td>
<td>5-20</td>
<td>350,000</td>
<td>2,000</td>
</tr>
<tr>
<td>D</td>
<td>100,000</td>
<td>5-20</td>
<td>3,500,000</td>
<td>20,000</td>
</tr>
</tbody>
</table>
Nonsterile Compounding: Guidelines for Healthcare Facility Pharmacies

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Nonsterile Compounding: Guidelines for Healthcare Facility Pharmacies

PREFACE

This is the 1992 edition of the Canadian Society of Hospital Pharmacists Nonsterile Compounding: Guidelines for Healthcare Facility Pharmacies. It is one of a series of documents establishing criteria for the practice of pharmacy in hospitals.

These Guidelines were developed to assist hospital pharmacists to assess current practices in bulk compounding and to develop appropriate procedures and controls relative to bulk compounding.

Bulk compounding is an integral part of hospital pharmacy practice. (See CSHP Standards of Practice.) Often the institution's goals and scope of medical staff practices require pharmacy's participation in research as well as in the development of unique dosage forms. This capability in pharmacy facilitates optimum medical management of patients.

These guidelines were approved under the title of Guidelines for Bulk Compounding of Products in Hospitals; the title was fine-tuned in 2009.

1. SCOPE

1.1

These Guidelines set forth procedures and controls to assist in assuring the quality of a bulk compound product.

1.2

These Guidelines are intended to include all nonsterile and sterile products prepared from raw materials. (Intravenous products prepared from commercially available injectable products are excluded). Sterile injectable products should also comply with the Intravenous Therapy Guidelines (see Bibliography).

1.3

These Guidelines were intended to augment but not replace the hospital's existing policies and procedures relative to bulk compounding.

2. GLOSSARY OF TERMS, ABBREVIATIONS, AND SYMBOLS

The following definitions apply for terms used in these guidelines. They may have different meanings in other contexts.

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bulk compounding</td>
<td>The preparation of products which are not commercially available, in anticipation of a physician’s order.</td>
</tr>
<tr>
<td>Commercially available (product)</td>
<td>A pharmaceutical product authorized for use in Canada by the Health Protection Branch, Health and Welfare Canada, and having received Notice of Compliance, has been assigned a Drug Identification Number (DIN) and marketed in Canada.</td>
</tr>
<tr>
<td>Master Formula</td>
<td>Set of instructions outlining in detail the materials, equipment, and procedures required to produce a specific quantity of a product.</td>
</tr>
<tr>
<td>WHMIS (Workplace Hazardous Materials Information Systems)</td>
<td>Federal and provincial legislation to ensure information regarding hazards of materials used in workplaces is provided to employers and employees.</td>
</tr>
</tbody>
</table>

CSHP Mission:
CSHP is the national voice of pharmacists committed to the advancement of safe, effective medication use and patient care in hospitals and related healthcare settings.
3. PERSONNEL

All bulk compounding should be conducted under the supervision of a pharmacist who possesses the knowledge, experience and ability to assume the responsibility for same. All personnel handling materials affected by the WHMIS legislation should receive the proper training.

4. PREMISES

The area designated for bulk compounding should:

a) be sanitary;
b) permit effective cleaning of all surfaces;
c) minimize the potential for contamination of the drug;
d) minimize the potential for the addition of any extraneous material; and

e) be conducive to the orderly flow of work.

5. EQUIPMENT

5.1

The equipment used in bulk compounding should:

a) permit effective cleaning;
b) minimize the potential for contamination of the product;
c) minimize the potential for the addition of extraneous material to the product;
d) be operated only for its intended use;
e) be subject to preventative maintenance procedures; and

f) be checked periodically for proper functioning and calibration.

5.2

Policies and procedures related to the use and maintenance of such equipment should be in accordance with the hospital's policies and procedures pertaining to occupational health and safety.

6. BULK COMPOUNDING CONTROL

6.1 Procedures

6.1.1

Written procedures should be in place for each bulk compounded product to ensure that the end product will meet the specifications for that product. A pharmacists shall assume responsibility for the final product and carry out appropriate checks at critical steps in the process.

6.1.2

The hygiene of all personnel participating in bulk compounding should be guided by policy and procedures within the department as well as the hospital employees' health and safety requirements.

6.1.3

Protective apparel may be appropriate to minimize contamination of the product during processing or packaging and to help protect the employee.

6.2 Master Formula

The master formula should indicate:

a) the name of product;
b) the dosage form of the product;
c) the specifications and source of each raw material used;
d) the formulation of each batch stating:
   i) weights and measures of each raw material; and
   ii) theoretical yield;
e) the equipment required;
Nonsterile Compounding: Guidelines for Healthcare Facility Pharmacies

f) a description of each step in the compounding process with special notations as required (e.g., which steps or measurements must be verified by a pharmacist or a second person);
g) the shelf life, when applicable;
h) the storage requirements;
i) specific packaging requirements;
j) a sample label, including WHMIS and auxiliary labeling where applicable;
k) the quality control testing to be performed, when applicable; and
l) reference sources for the formula, stability data, if available.

6.3 Production Records

6.3.1

A separate production record should be used for each batch compounded.

6.3.2

The production record should include:
a) the date of compounding;
b) the lot or batch number assigned to the compounded product;
c) the manufacturer’s name and lot number of each raw material used;
d) a provision for sign-off of each step in the compound for the person compounding and the person checking;
e) the process, including weights and measures performed;
f) the results of all quality control testing;
g) a statement of final yield;
h) signatures for final verification and authorization for release;
i) a sample label; and
j) the expiry date of the product.

6.4 Raw Material

6.4.1

The quality and identity of all raw materials used in bulk compounding should be verified using a certificate of analysis from the chemical supplier or the label claims of commercially available products used in the compounding process.

6.4.2

Specifications should be of pharmacopoeial or equivalent status.

6.5 Labelling

The labelling of the finished product should be permanent and contain descriptive information including:
a) the name of product;
b) the strength of product;
c) the dosage form of product;
d) the lot or batch number;
e) storage conditions, when applicable;
g) the expiry date;
h) auxiliary labels; and
i) WHMIS labelling where applicable.

6.6 Packaging

The packaging of the finished product should:
a) be appropriate for the dosage form;
b) protect the product from light and moisture as necessary;
c) minimize the potential for interaction between the drug and the container; and
d) be sterile and free from particulate matter for sterile products.
6.7 Record Keeping

Records should be kept for an appropriate period of time in compliance with hospital procedures.

Note: The Good Manufacturing Practices for Drug Manufacturers and Importers, Health and Welfare, Canada, suggests a period of one year after the expiration date on the label of the compounded product.

6.8 Reporting

Hospitals should comply with all reporting regulations required by the Health Protection Branch.

6.9 Quality Control

6.9.1 Premises

Written procedures for cleaning the bulk compounding area should include:

a) the cleaning interval;
b) cleaning agents and their concentrations; and
c) disposal of waste material and debris.

6.9.2 Equipment

Routine equipment maintenance, calibration, and certification should be defined, documented, and carried out.

6.9.3 End Product Testing

6.9.3.1 Nonsterile Products

Appropriate end product testing methods should be performed.

6.9.3.2 Sterile Products

Sterility tests should be performed on bulk compounded sterile products.

7. BIBLIOGRAPHY


WHMIS - see federal Bill - C-70 and provincial legislation on Occupational Health and Safety.