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' 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 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 pharmaceutical 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,
  (iv) lot number determination;
(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 Certficiate 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 ante-room 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 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 sanitation 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 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:

(a) for patient-specific products - the patients name; location (when applicable);
(b) for batch products - the control or lot number;
(c) reference number of the prescription or medication order (when applicable);
(d) generic ingredients and vehicle names, quantity, and concentrations (when applicable);
(e) date (and where applicable, time) of preparation;
(f) expiration date (and where applicable, time);
(g) prescribed administration regimen, when appropriate (including rate and route of administration);
(h) auxiliary labelling (including precautions);
(i) storage requirements;
(j) identification of all pharmacy personnel involved in product preparation and dispensing;
(k) name, address and phone number of the pharmacy for outpatient products;
(l) device specific instructions (when appropriate [e.g., with patient controlled analgesia devices]); and,
(m) any additional provincial or federal requirements.

11.2
The label should be legible and when possible affixed to the final container in a manner enabling it to be read while the sterile product is being administered

11.3
The label should be checked by a pharmacist or delegate against the original order (or pharmacist-verified copy) for accuracy and completeness.

11.4
Intermediate or in-process products shall be clearly labelled and where appropriate, the product or batch should be labelled to indicate the stage of production or status of the contents (e.g., quarantined, accepted, rejected).

11.5
Procedures shall be instituted to ensure labels for different batches or products are separated and controlled so as to avoid cross-labelling.

12. PROCESS VALIDATION

12.1 General principles

12.1.1
Process validation involves the establishment of scientifically sound compounding procedures that, if followed, ensure the drug meets all appropriate specifications for identity, strength, quality and purity.

12.1.2
Deviations from these established procedures should be minimized and, before they are implemented, should be documented and approved by the designated pharmacist.

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.

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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

GRADE	U.S. FED STD 209D	AIR CHANGES PER HOUR	MAX. PERMITTED NO. OF PARTICLES PER m^3 EQUAL TO OR ABOVE		MAX. PERMITTED NO. OF VIABLE MICROORGANISMS PER m^3
			0.5 um	5 um	
A laminar air flow work station	100	flow of 0.3 m/s (vertical) or 0.45 m/s (horizontal)	3,500	0	less than 1
B	100	5-20	3,500	0	5
C	10,000	5-20	350,000	2,000	100
D	100,000	5-20	3,500,000	20,000	500