

SHPA Guidelines for Medicines Prepared in Australian Hospital Pharmacy Departments

SHPA Manufacturing Working Party

These are guidelines of professional practice and not standards prepared or endorsed by Standards Australia. They are not legally binding.

INTRODUCTION

These guidelines supersede the National Coordinating Committee on Therapeutic Goods' Standard for the preparation of pharmaceuticals in Australian hospital pharmacy departments, and the Society of Hospital Pharmacists of Australia (SHPA) Guidelines of practice for aseptic dispensing services.^{1,2}

SHPA endorses the Pharmaceutical Inspection Co-operation Scheme (PIC/S) Guide to good practices for preparation of medicinal products in healthcare establishments, as the standard for medicines prepared in Australian hospital pharmacy departments.³ These SHPA guidelines **must** be read in conjunction with the PIC/S Guide, as well as existing Australian standards, codes or guidelines and elaborated by local procedures or practice guidelines. These SHPA guidelines provide detail and instruction to assist with implementing the PIC/S Guide for Australian hospital pharmacy practice and follow the same format as the PIC/S Guide.

Hospital pharmacy departments that are unable to comply with these guidelines because of infrastructure limitations should develop and implement a risk-management plan. This plan should focus on procedural and quality assurance measures to achieve a similar outcome as facilities that comply with these guidelines.

SCOPE

These SHPA guidelines are applicable to:

- all types of medicines prepared in Australian hospital pharmacy departments;
- aseptic and non-aseptic preparation;
- immediate-use products for individual patients to batches of products made in advance;
- procedures such as labelling and re-packaging to aseptic manipulation; and
- medicines prepared by externally contracted pharmacists servicing hospitals and nursing homes.

Australian hospital pharmacy departments licensed by the Therapeutic Goods Administration may need to comply with additional requirements.

For cytotoxic preparation, the SHPA Standards of practice for the safe handling of cytotoxic drugs in pharmacy departments, and the International Society of Oncology Pharmacy Practitioners' Standards for safe handling of cytotoxics, should also be consulted.^{4,5}

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GENERAL REQUIREMENTS

Pharmacy departments that prepare non-aseptic, aseptic, batch and single-use products require:

1. appropriately trained personnel;
2. procedures for purchase of materials, safe handling, warehousing and storage;
3. processing instructions (specification, volume calculation, instruction, expiry, storage, record) to collect all ingredients required to prepare the product, prepare labels and confirm quantity of ingredients (for preparation);
4. double-check (where possible) of ingredients, labels and orders; as well as all weighing (tare, final weight) and volumes;
5. a suitable environment, correct technique, appropriate equipment and processing instructions;
6. double-check (where possible) of final product accounting for all ingredients, including remaining ingredients and labelling of product;
7. to retain documentation as record of preparation according to local requirements; and
8. appropriate safety packaging and made ready for transportation.

QUALITY ASSURANCE

*PIC/S Guide (Chapter 1).*³ The objective is to produce a consistently safe and effective product for every patient, known or unknown, irrespective of its scale or complexity. Quality assurance is assisted by implementing a quality management system as defined in the AS/NZS ISO 9000.⁶ These standards will guide implementation and operation of an effective quality management system for the preparation of medicines in hospitals. They also apply to the preparation of medicines by externally contracted pharmacists servicing hospitals and nursing homes.

PERSONNEL

*PIC/S Guide (Chapter 2).*³

Responsible Pharmacist

The Director of Pharmacy must designate a pharmacist to be in charge of the preparation area who will be responsible for overall management. This pharmacist will be responsible for developing work sheets, verifying prescriptions, final check and release of products and clinical decisions. A deputy should be nominated in case the responsible pharmacist is absent.

Production Supervisor

The Director of Pharmacy must designate a person in charge of the preparation area (Production Supervisor) who has overall responsibility for quality management.

This person may be a pharmacist or suitably qualified technician. Suitable qualifications may include certificate IV for pharmacy technicians or an overseas accredited course.

If necessary, a Production Supervisor should be designated to each preparation area, aseptic and non-aseptic, e.g. Aseptic Production Supervisor. A pharmacist may combine the roles of Responsible Pharmacist and Production Supervisor.

Regularly reviewed and updated job descriptions should be available, which detail responsibilities of the position and reflect commitment to quality management principles. There should be an organisation chart depicting the hierarchy and reporting structure.

There should be an adequate number of competent personnel in the preparation area.⁷ When there are no guidelines from a registering authority, the ratio of two pharmacy technicians to one pharmacist should not be exceeded.⁸

Consideration should be given to the maximum safe workload for aseptic unit staff.^{9,10} The risk of errors increases if staff work beyond safe capacity. Limits should be set depending on the size of the unit and the number of staff. Where possible, each unit should define their maximum output to ensure patient safety and this should be agreed by senior management.

The Aseptic Production Supervisor should complete an accredited training course in aspects of aseptic dispensing, including standards for facilities, equipment and staff, pharmaceutical microbiology, aseptic transfer techniques and quality assurance. They must have relevant knowledge and current practical and theoretical experience in preparing aseptic products. The Aseptic Production Supervisor should have an understanding of certification requirements, clean area and clean air device technology and a thorough knowledge of all the design features in their department, e.g. heating, ventilation and air conditioning systems, position and grade of HEPA filters, types of work station, isolator design.

Operator Training

Training for personnel involved in any preparation should include:

- awareness of the consequences of deviation from validated processes and standard operating procedures, to the product integrity and the patient;
- an appropriate level of general good manufacturing and good preparation practices;
- local safety practices including occupational health and safety;
- principles of quality management relevant to the activities for personnel who are qualified or undergoing qualification;
- operator validation in aseptic areas (Appendix 2);
- orientation and training for new staff; and
- ongoing and documented system of continuing education and training.

Hygiene

*PIC/S Guide (Chapter 2, Section 4).*³ Personnel involved in the preparation of medicines must maintain high standards of personal hygiene and cleanliness. They must report any condition (e.g. diarrhoea, coughs, colds, infected or infested skin or hair, wounds) that may result in the shedding of abnormal numbers or types of

contaminants. There should be a procedure for assessing the fitness of personnel by the Production Supervisor with regard to infectious diseases and open lesions.

Artificial (acrylic) nails must not be worn during aseptic preparation and should be covered by gloves during non-aseptic preparation.¹¹ Make-up should not be worn during aseptic preparation.

Personnel with chronic disease or conditions that may present an increased microbiological hazard to products must not work in aseptic preparation areas. The Production Supervisor should decide the nature of the action taken.

Visitors should be subject to the same procedural rules as staff if their presence could compromise the quality of the product. Visitors should be discouraged from entering aseptic preparation areas but if allowed entry they should be subject to the same health rules as applied to staff

Written procedures must be available to ensure the achievement, maintenance and regular monitoring of required standards of hygiene and cleanliness.

Hand Washing

The objective of adequate hand washing is to provide clean (not 'sterile') hands with almost all debris removed.

Non-Aseptic Preparation

1. Remove jewellery and nail polish.
2. Wash hands with an antimicrobial skin cleaner (chlorhexidine 4% w/v) or disinfectant (povidone-iodine) for 10 to 15 seconds.
3. Clean all surfaces of the hands and wrists without excessive abrasion. A brush may be used to remove debris from beneath nails (if necessary).
4. Do not touch taps with clean hands. Use paper towels to touch taps if elbow/foot controls are not available.
5. Dry hands either in the air or physically with a low-linting disposable towel.
6. Wear gloves if there is potential to contact exposed product or the product is potentially hazardous.

Aseptic Preparation

1. Remove jewellery and nail polish.
2. Wash hands with an antimicrobial skin cleaner (chlorhexidine 4% w/v) or disinfectant (povidone-iodine) for one minute.
3. Clean all surfaces of the hands and wrists without excessive abrasion. A brush may be used to remove debris from beneath nails (if necessary).
4. Do not touch taps with clean hands. Use paper towels to touch taps if elbow/foot controls are not available.
5. Dry hands either physically with a low-linting disposable towel or in the air using a hand drier designed for cleanroom use.
6. For aseptic preparation, sterile alcohol 70% or alcohol gel 70% may then be applied prior to gloving.
7. For working in a clean work station, gloved hands should be regularly surface disinfected with a small quantity of sterile alcohol 70%.

Also refer to the Commonwealth Government's Infection control guidelines (Section 12-1).¹¹

Clothing

Personnel must be issued with clothing suitable for the level of preparation. Suitable footwear with closed toes should be worn for all preparation. For non-aseptic preparation, gloves and mask must be worn when there are risks to the operator or product. Alternative gloves should be available for personnel with latex allergy. For cleanroom garment requirements see Appendix 2.

Occupational Health and Safety

Hazardous substances are those that following worker exposure can have an adverse effect on health.¹² Staff may be required to handle hazardous substances, e.g. strong acids, formaldehyde or antibiotic tablets that release dust when crushed. Appropriate measures must be taken to protect staff from exposure to these substances such as provision of a fume or powder cupboard, protective masks and goggles.

Material safety data sheets for hazardous substances that are handled should be available for reference. This also applies to commercial pharmaceuticals modified for manufacture, e.g. crushing tablets.

All staff engaged in cytotoxic preparation must be advised of the risks of exposure. They should have regular medical examinations to assist in the monitoring of this exposure, with results maintained in their medical record. Individual records should be kept of all exposures to cytotoxics as specified in the SHPA's Standards of practice for the safe handling of cytotoxic drugs in pharmacy departments.⁴

Also refer to local occupational health and safety guides for handling hazardous materials, e.g. Worksafe Victoria's Handling cytotoxic drugs in the workplace.¹³

Records

Maintain staff records of:

- training specific to each staff member;
- their signatures against their names; and
- their exposure to cytotoxics (as above).⁴

Maintenance and Service Staff

Cleaning and maintenance staff should receive regular training in relevant procedures. For example, hygiene, basic microbiology and advice on the hazards of exposure to cytotoxics. When external staff who have not received such training (e.g. building, maintenance contractors) are brought in, care should be taken over their supervision.

PREMISES AND EQUIPMENT

*PIC/S Guide (Chapter 3).*³ Preparation areas should provide:

- sufficient space with separation of activities;
- sufficient light, controlled temperature and humidity;
- air supply of appropriate particulate level;
- air pressure differentials with adjoining areas (where necessary); and
- directional control of airflow and air exchange rates.

Separate preparation areas for different dosage forms (e.g. dry and wet production) is ideal. If not possible, a documented risk assessment performed and appropriate measures taken, before handling different dosage forms at the same time.³

To avoid cross-contamination weighing and sampling areas should be sufficiently separate from other preparation areas.³

There should be a dedicated facility for handling hazardous products with validated cleaning procedures between different classes of products.³

Specialised facilities, such as cleanrooms and clean work stations, must comply with the relevant Australian standards (testing and certification).¹⁴ For requirements of cleanroom premises see Appendix 2.

Equipment

- Equipment must be kept clean, dry and protected from contamination when not in use.
- Equipment should be inspected for cleanliness and (where necessary) cleaned and decontaminated before the start of any operation.
- Specific written instructions for cleaning should be available at the point-of-use.
- Programs and procedures should be developed for testing and calibration of measuring, weighing and control equipment, and appropriate records kept.
- Equipment should be available to monitor the cleanroom environment, e.g. manometers to measure air pressure differentials, alarms to indicate failure of air supply, air and surface samplers to determine particulate and microbial contamination. Procedures for the use of such equipment and the interpretation of results should be available. Regular physical, environmental and microbiological testing must be carried out as outlined in the *PIC/S Guide (Appendix 2, Section 6)*.³
- Equipment must be maintained in accordance with written procedures. Records of maintenance should be kept wherever the maintenance or lack of it may affect product quality
- Equipment used for terminal sterilisation of products and equipment, e.g. steam or gas sterilisers and sterilising ovens, should comply with the *PIC/S guide for good manufacturing practice for medicinal products* and Australian standards.^{15,16}

DOCUMENTATION

PIC/S Guide (Chapter 4) outlines principles, general requirements and documentation needed for different types of preparations and lists written procedures that should be available.³

All documentation and labelling should comply with local regulations and guidelines. See Appendix 1 for detailed requirements for Australian hospitals.

A system of double-checking should be developed and recorded to ensure (where possible) that two people are always involved (one preparing and the other checking).

PRODUCTION

*PIC/S Guide (Chapter 5).*³ There should be sufficient staff and written procedures to ensure that for all re-packaging and preparation (where possible) there is double-check of:

- primary materials, labels and orders;
- all weighing (tare, final weight) and volumes; and
- final product accounting for all primary materials, including remaining materials and labelling of product.

Expiry Dates

All re-packaged or prepared products must include an expiry date on the label. Product stability information should be well documented and include referenced publications and validated local data. The expiry date is the end of the shelf-life period after which the product should not be used.

Re-Packaged Products

The expiry date should be the manufacturer's expiry date or one year from re-packaging, whichever is sooner. This is dependent on the container used being equivalent to the manufacturer's container. Re-packaged tablets or capsules in blister packs may use the manufacturer's expiry date.

The expiry date for re-packaged extemporaneously prepared items is the date allocated at the time of preparation.

Non-Aseptic Prepared Products

The expiry dates described below can be used in the absence of stability data applicable to a drug and preparation when stored in tight light-resistant containers and at controlled-room temperature (unless otherwise indicated). Longer expiry dates should be supported by local validation studies or referenced publications.¹⁷

For non-aqueous liquids and solids, the default expiry date should not be more than 6 months. If a manufactured product is the source of drug, e.g. crushed tablets, then the expiry date should be 25% of the products expiry date or 6 months (whichever is earlier).¹⁷

For aqueous products without preservatives and microbiological testing, the default expiry date should be a maximum of 7 days when stored at 2 to 8 °C (if the chemical stability is known).

For aqueous products with preservatives, the expiry date should be based on chemical stability. The expiry date should be a maximum of four weeks as per the *Australian Pharmaceutical Formulary and Handbook*.¹⁸

If chemical stability is not known, instead of aqueous solutions consider making capsules or powder sachets.

For all other formulations, the default expiry date should not be greater than the intended duration of therapy or 30 days (whichever is earlier).¹⁷

Aseptic Prepared Products

Due to the risk of microbial contamination, the default expiry date for aseptic products without sterility tests should be 24 hours, which may be extended to 7 days provided the product is:

- prepared in a validated Grade A Laminar Air Flow Work Station (LAFWS);
- prepared by suitably trained and validated personnel; and
- physically and chemically stable.

Longer expiry dates should be supported by local validation studies or referenced publications.¹⁹ Relative risk assessments for aseptic products are described in Table 1. When the expiry date differs between storage at 2 to 8 °C and use at room temperature, the product should be adequately labelled to alert users of the storage requirements.

Table 1. Relative risk assessment of aseptic products

Aseptic solutions	Demonstrated microbial contamination potential	Demonstrated occupational exposure hazard	Risk of compounding error	Chemical incompatibility, instability risk
Parenteral nutrition solutions containing lipid emulsions and cardioplegic solutions prepared on an item-by-item basis	low ²³	none	moderate ²⁴	high ²⁵
Parenteral nutrition solutions containing lipid emulsions and cardioplegic solutions prepared in batches by pooling contents of several original containers	high ²⁶⁻³¹	none	high	high ²⁵
Lipid emulsions, propofol and liposomal drugs not in combination with other solutions prepared on an item-by-item basis	moderate ³²	none	low	low
Lipid emulsions, propofol and liposomal drugs not in combination with other solutions prepared in batches by pooling contents of several original containers	high ³³	none	low	low
Cytotoxics, immunosuppressants, genotoxic agents	low ³⁴⁻³⁶	high ^{37,38}	high	low
Epidural, intrathecal injections prepared on an item-by-item basis	moderate	none	moderate	low
Epidural, intrathecal cytotoxic injections prepared on an item-by-item basis	moderate	high	high	low
Epidural, intrathecal injections prepared in batches by pooling contents of several original containers	high	none	moderate	low
Antibiotic solutions	low	moderate	low	moderate
Sterile solutions (non-cytotoxic) in elastomeric infusion pumps; other ambulatory infusion devices	low	moderate	moderate	high
Large and small volume infusion solutions, prefilled syringes (non-cytotoxic)	moderate	none	moderate	moderate
Irrigations for body cavities (non-cytotoxic), wounds	moderate	none	low	low
Ophthalmic solutions (non-cytotoxic)	moderate	moderate	moderate	low

For aseptic solutions having a high risk of microbial contamination in conjunction with a high risk of chemical incompatibility, consider contracting the preparation to TGA-licensed providers, either commercial or to hospitals specifically TGA-licensed for the purpose.

If sterility testing is performed, the expiry date can be determined from the chemical and physical stability of the final product according to scientific studies, published references or correspondence with manufacturers. The expiry dates recommended for non-aseptic prepared products may then be used.^{17,19}

Also refer to the US Pharmacopeial Convention (chapters 797, 795); European Medicines Agency's Quality risk management; Therapeutic Goods Administration's Australian regulatory guidelines for prescription medicines; and Quality assurance of aseptic preparation services.¹⁷⁻²²

Raw Ingredients

*PIC/S Guide (Chapter 5, Section 5).*³ Raw ingredients should be procured to established specifications as detailed in the Master Record sheet. They should comply with pharmaceutical grade specifications (if possible), e.g. BP, USP. If making injections then injectable grade ingredients are preferable.

Quarantine raw materials before use and ensure a system of labelling to identify raw material in quarantine as opposed to those released after inspection/testing.

At the point of receipt, the raw material container should be visually examined. Particular attention should be paid to raw material packed in plastic or paper bags and to containers visibly soiled by liquid. Any damage or contamination likely to prejudice the integrity of the contents should be reported and assessed by a nominated pharmacist. All rejected material should be destroyed or quarantined and clearly marked 'rejected' for return to the supplier.

A recording system should be in place that allows traceability of all material at all stages, i.e. from the patient who receives the product, to the material, to the supplier.

Although it would not normally be expected that hospital pharmacies carry out their own testing of raw material, it is expected that a system be established to ensure that all material meet the required specification at the time of receipt and throughout the period of use. This system should include:

- purchasing raw material from a reliable supplier of known origin, based on a history of deliveries which satisfied all specifications;
- valid certificates of analysis (provided by the supplier); and
- testing and analysis, in-house or contracted, where considered necessary.

Raw material not given an expiry date by the supplier must be given a shelf-life. If there is a need to extend the shelf-life at the end of this period, the raw material must be validated for further use. The shelf-life will be arbitrary and to an extent based on knowledge of the material and supported by local data.

For material with short in-use expiry dates, the date of first opening should be indicated on the container.

Raw material should be stored and used under appropriate conditions. If transferred to other containers, these should be clean and labelled with batch-specific information. Mixing of different batches is prohibited.

Water used as an ingredient should be purified before use or purchased sterile. Purified water should be tested frequently to demonstrate acceptable microbiological quality. Refer also to *PIC/S Guide (Annex 2)*.³

Non-Aseptic Liquids, Creams and Ointments

PIC/S Guide (Annex 2) outlines general requirements for the preparation of liquids, creams and ointments.³

Packaging Material

*PIC/S Guide (Chapter 5, Section 7).*³ Labels and packaging materials should also be subject to quality control procedures.

Empty containers should be accepted only if packed to exclude dust or other contamination in transit and stored to prevent contamination on storage. Containers and closures should be selected with the following considerations:

- compatibility and fit of individual components;
- protecting the product from light and moisture;
- preventing contamination of the product, including microbial contamination (when necessary);
- preventing deterioration of the product through chemical reaction with either the material of the containers or substances leached from the containers or through loss of substances from the containers;
- compliance with official requirements for the packaging of products, e.g. child-resistant closures and tamper-evident measures; and
- appropriate size and type for product concerned.

Labelling

Labels should be of sufficient material and printing quality, and size to ensure identification and permanence. Labels should contain the following typewritten or printed information:

- approved name and strength of product, and for extemporaneous products the full list of ingredients including excipients;
- batch number or identification number;
- storage conditions (where necessary);
- expiry date and (where appropriate) time of expiry;
- quantity of preparation, i.e. volume, weight or count (for aseptic products it is the final volume including the volume of all additives);
- name and address of pharmacy; and
- other wording as per legal or hospital requirements.

Packaging Operations

*PIC/S Guide (Chapter 5, Section 8).*³ For packaging operations ensure that mistakes do not occur during labelling. Attention should be paid to label security storage and verification of label text with the information on the master process record. All unused batch-coded labels should be destroyed. Before commencing any labelling operation, ensure that all materials, labels and products of previous operations are removed.

For non-batch preparation, at least two people should sign that labels are checked and product labelled correctly.

For batch preparation, a system of reconciliation of labels must be documented. For complex packing and labelling and wherever equipment should be inspected for residual product, the documentation should include space for signature verifying that all materials, labels and product from previous operations have been removed and equipment inspected.

The control or batch number system used should give ready access to all information required to establish the integrity of ingredients and the procedures used in preparing the finished products. The method of batch numbering should be documented.

QUALITY CONTROL

*PIC/S Guide (Chapter 6).*³

Physical and Chemical Stability Testing

Physical and chemical stability testing is not required for most products made in hospital pharmacy departments. This is due to the availability of stability data and the expected short use-by period. However, when stability data are not available, and the pharmacy is compounding batch quantities for extended use, then stability testing should be performed. A guideline to the design of a stability testing program is available.²¹

Sterility Testing and Validation

Terminally Sterilised Products

*PIC/S Guide (Annex 1, Section 4).*³ Refer also to the Therapeutic Goods Administration's Guidelines for sterility testing of therapeutic goods.³⁹

Aseptic Transfer Products

Aseptic transfer is the process of manipulating aseptic starting material to transfer singly or in combination to aseptic delivery systems for administration to patients in a manner that excludes the entry of microorganisms, particles and endotoxins. The quality of aseptic solutions produced by aseptic transfer is assured by ensuring:

- starting materials are manipulated only within the Grade A controlled environment;
- manipulation is performed by trained and validated operators;
- standard operating procedures are complied with; and
- all relevant sections of these guidelines are observed. Materials are manipulated in a low-risk environment, and most of the processes are of low to moderate risk of microbial contamination. There is no requirement for sterility testing of aseptic products produced by aseptic transfer. Sterility testing of these products is inappropriate for a number of reasons:
 - any contamination that may occur is likely to be with small numbers of microbes. The probability of detecting a contaminated unit from a single sterility test is impractically low (Table 2);

Table 2. Probability of detecting a contaminated lot in a single test

Sample size	Percentage of items contaminated			
	0.1%	1%	2%	5%
10	0.01	0.09	0.18	0.40
20	0.02	0.18	0.33	0.65
50	0.05	0.39	0.64	0.92
100	0.09	0.63	0.87	0.99

- small numbers of microbes introduced into parenteral solutions may flourish, may not multiply or may die, rendering any subsequent testing inconclusive;⁴⁰⁻⁴²
- specialised training in pharmaceutical sterility testing is required to perform this work reliably. The sterility test must be performed at a higher level of sterility assurance than the process it seeks to evaluate. This may be difficult in hospital laboratories;
- sterility testing of bulk-prepared products in the hospital pharmacy has not always detected contamination;^{28,29}

- attempts to sterility test solutions containing cytotoxics pose an hazard to personnel conducting the test and personnel in the near vicinity; and
- sterility testing requires 14 days incubation in a number of cases, this exceeds the shelf-life of the solutions.⁴³ Returned unused solutions may be used for retrospective sterility tests providing the integrity can be assured.

Pyrogen Testing

Unless the nature of the product makes pyrogen testing impossible, pyrogen testing should be carried out on all batches of parenteral products and solutions for irrigation of body cavities, wounds, operation cavities or the urogenital system where:

- the volume to be administered or used in a single or application dose is 15 mL or more; or
- the label on the container indicates that the preparation is apyrogenic; or
- directed by a statutory requirement.

Pyrogen testing should be replaced by testing for bacterial endotoxin wherever practicable and approved.⁴⁴

CONTRACTED WORK

PIC/S Guide (Chapter 7) outlines principles, general requirements and responsibilities of both contract giver and acceptor.³ Refer also to the *Therapeutic Goods Regulations 1990 Schedule 5A*, for requirements regarding the manufacture of medicines by others outside of the hospital.⁴⁵

COMPLAINTS AND PRODUCT RECALLS

PIC/S Guide (Chapter 8) outlines principles, quality problems and recall procedures.³

SELF AUDITS

PIC/S Guide (Chapter 9) outlines the principles of a self-audit program.³ A sample audit tool based on the UK QCP-71 document will be developed and made available on the SHPA web site.

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APPENDIX 1. Documentation for products prepared regularly or for stock

Master processing records need to include the items described below.

SPECIFICATIONS

Specifications for ingredients and (where applicable) packaging materials should include:

- name (such as pharmacopoeial reference);
- description;
- procedures for sampling and testing with references;
- qualitative and quantitative requirements with acceptance limits;
- storage conditions and precautions; and
- shelf-life.

Specifications for intermediate or finished products should include:

- name;
- description of dosage form and strength;
- formula, i.e. a standard formula reference and/or a list of ingredients with the amount of each ingredient per dosage unit, per unit of weight or measure of the finished product, and a statement of the total weight or measure of such dosage unit. When material of variable potency is used a place for the relevant calculation;
- package details;
- instruction for sampling and testing, or a reference to procedures;
- qualitative and quantitative requirements with acceptance limits;
- storage conditions, microbiological requirements and precautions (where applicable); and
- expiry date.

INSTRUCTIONS

Processing Instructions

Processing instructions should include:

- product name;
- dosage form and strength;
- batch size;
- type and quantity of all starting materials;
- expected yield of intermediate or finished product;
- a statement of the equipment to be used and any steps to be taken in preparing the equipment (e.g. cleaning, assembling, calibrating, sterilising);
- detailed stepwise instructions, e.g. order of adding ingredients, mixing specific ingredients prior to adding to the base;
- instructions for in-process controls with acceptance limits; and
- storage conditions (also for intermediate products) and precautions (where applicable).

Packaging Instructions

Packaging instructions should include:

- product name;
- dosage form and strength;
- package size;
- labelling text or master label and any advisory labels;
- list of all necessary packaging materials, including type, specification, size and quantity;
- detailed stepwise instructions;
- instructions for in-process controls with acceptance limits; and
- storage conditions (also for intermediate products) and precautions (where applicable).

RECORDS

Processing and Packaging

Processing and packaging records should include:

- qualitative and quantitative information of all materials used, such as batch numbers or other references, enabling traceability to further quality-related documents (e.g. product, number of analysis, number of certificate);
- identification of the product (including batch number and preparation formula) and the date of preparation;
- information on all operations and observations, such as documentation of cleaning, line clearance, weighing, yields of intermediate steps, readings and calculations, as well as sampling;
- records on batch-specific in-process controls and results obtained;
- initials or signature of the responsible operators for significant processing steps and controls. When this person is not a pharmacist then the signature of the pharmacist checking;
- deviations from the approved processing instruction;
- yield of finished product;
- yield or reconciliation of bulk and packaged product;
- expiry date of finished product;
- sample label;
- reconciliation of labels, signature to verify destruction of all unused batch-coded labels; and
- name of patient or a unique batch or other identifying number (where applicable).

Processing records should be finally assessed and approved by the responsible person or releasing officer dating and signing.

Quality Control Records

Quality control records should include:

- product name;
- dosage form and strength;
- batch number;
- preparer or supplier;
- testing method (any deviations from the method should be justified);
- test results (certificate of analysis from preparer or supplier including date of the test, where applicable);
- expiry date of starting material;
- date of the test;
- initials of the person performing the test; and
- decision on release or rejection including the initials of the responsible person or release officer.

Repackaging Records

Master Process Record should include:

- generic name and strength of the product;
- quantity per pack;

- labelling requirements with a sample label and any advisory labels;
- type of container and closure;
- adequate working instructions;
- usual number of packs to be packed;
- published references to support formulation and expiry dates; and
- sufficient space on the form to record the details as shown below in the Batch Record.

The Batch Record may be a copy of the Master Process Record and should include:

- date of packing;
- name and signature of the person repacking;
- generic and brand name, and strength of the product;
- name of the manufacturer and manufacturer's batch number or hospital batch number;
- type of container;
- quantity of product remaining;
- yield or reconciliation of bulk and packaged product;
- a sample label;
- expiry date (either the manufacturer's expiry date or for extemporaneous products the date set by the hospital pharmacy at the time of preparation);
- name and signature of the pharmacist preparing or checking the batch; and
- signature to verify destruction of unused batch-coded labels.

APPENDIX 2. Aseptic procedures

*PIC/S guide (Annex 1).*³

PREMISES AND EQUIPMENT

PIC/S guide (Annex 1, Section 2) and AS/NZS ISO 14644.4:2002.^{3,14} Clean areas for preparing aseptic products are classified in four grades (A, B, C, D) according to the required characteristics of the environment. The room classification grade is dependent on the activities performed and the products prepared. Figure 1 illustrates the basic requirements for standard aseptic manipulation of aseptic fluids. When hazardous solutions, e.g. cytotoxics, are manipulated, containment of the active materials is an additional requirement, and air pressure gradients must operate in a more complex manner.

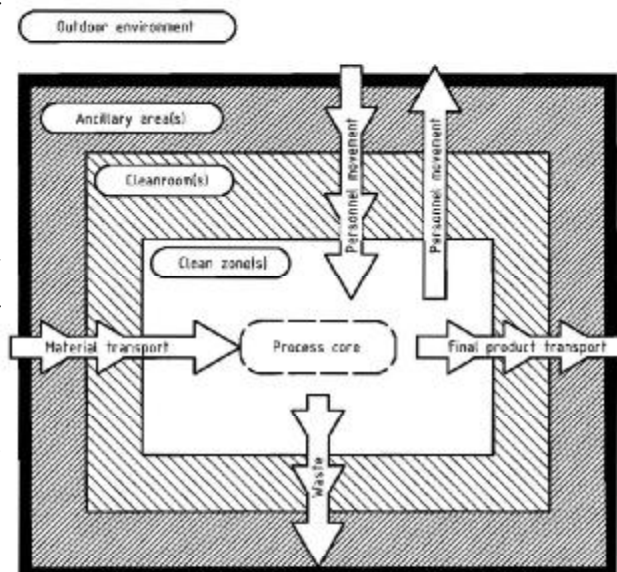


Figure 1. Shell-like contamination control concept.¹⁴

Premises should be structurally suitable for the establishment of controlled environments and be located in facilities compatible with preparation of aseptic products. Secure areas required to support the operation of cleanrooms should be adequate in size and provide direct access to cleanrooms.

Aseptic facilities complying with PIC/S are ideally four zone systems.³ When at rest, the air quality within the cleanroom must be equivalent to the Grade A LAFWS. When the room is in use by the maximum number of operators for which it is designed, air quality must not fall below Grade B. All zones opening onto the cleanroom must be maintained at Grade B. Figure 2 illustrates the four zone system.

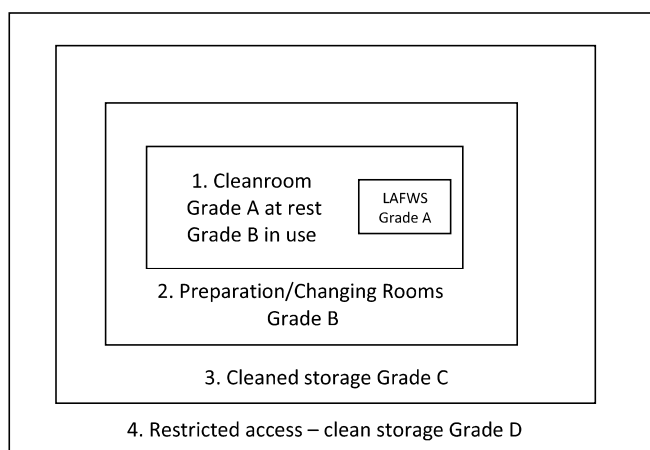


Figure 2. Room classification of the four zone system.

Aseptic facilities need to include:

- an area for receiving and checking incoming starting materials, with a separate space for removal of outer packaging;
- an area for storage of starting materials (temperature monitored refrigeration and freezer storage if required);
- an area for computers and printers in which documentation (labels, worksheets, reference documents, records) are prepared and stored;
- controlled environments where starting materials are decontaminated, assembled and passed directly into the cleanrooms;
- changing rooms to remove outdoor clothing which do not lead directly to Grade B and C areas;
- changing rooms linked directly to the cleanrooms in which cleanroom garments are donned;
- hand washing and drying facilities including non-touch taps. These should not be installed in the rooms connected directly to the Grade A/B rooms;
- cleanrooms, recommended at zone A at rest or B during operation;
- areas for reconciliation and packaging of finished products, also linked directly to the cleanrooms. The bench space allocated for these tasks should be large enough to ensure that materials from one order cannot be mixed up with other orders;
- refrigeration/freezing space for interim or short-term storage of completed solutions; and
- space in which cleaning materials can be safely stored.

In most cases, rebuilding existing aseptic facilities to meet these more stringent requirements is not a practical option in the near term, so other means need to be considered to meet Grade B air quality in the cleanroom while in operation. These may include:

- review of cleaning methods and frequency of cleaning;
- removal of all but essential items from the cleanroom;
- replacing conventional solid shelved trolleys with chromed mesh trolleys and replacing plastic bins for mesh bins for needles, syringes and other essential accessories (e.g. transfer devices, filters);
- introducing needles, syringes and other essential accessories in quantities sufficient **only** for a particular preparation;
- review of the quality and types of cleanroom garments in use; and
- inspection and repair of any surface wear or damage on floors, walls and ceiling.

For the preparation of cytotoxics, measures must be taken to protect the operator from the materials being handled. For cytotoxic drugs refer to the SHPA Standards of practice for the safe handling of cytotoxic drugs in pharmacy departments.⁴

Clothing

For cleanroom garment requirements see *PIC/S Guide (Annex 2, Section 2)*.³ Also refer to the hygiene and handwashing sections of this guideline.

Outdoor clothing should not be brought into changing rooms leading to Grade C and B areas.³ This can be achieved by either:

1. removing outdoor clothing in a changing room in the Grade D area and changing into a non-sterile, low-linting coverall (undergarment) or coat/pants before entering the change room leading to Grade C and B areas. This should be worn with high overshoes with the trousers tucked in. This coverall would then be covered in the change room prior to entering the Grade A/B area with the cleanroom coverall, hood and boots. ‘Theatre scrubs’ are not suitable for cleanroom apparel because they leave large areas of the operator’s skin exposed, do not prevent perineal shedding and are prolific generators of cotton particles. Additional costs associated with this approach might be creation of a changing room affording privacy in the Grade D area, provision of lockers for street clothes and the cost of the low-linting coverall or coat/pants and laundering; or
2. covering lightweight outdoor clothing entirely with a non-sterile, low-linting coverall or coat/pants before entering the changing room leading to Grade B and C areas. This should be worn with high overshoes with the trousers tucked in. The outdoor clothing should be a lightweight shirt or blouse and pants (not skirts). All other exterior clothing (e.g. jackets) are removed in the Grade D area. On entering the changing room to the Grade A/B areas, the coat is hung on the outer wall of the step-over zone. The outdoor clothing is momentarily exposed while donning the cleanroom coverall, hood and boots.

Hazardous Products

Dedicated clean areas are recommended for more hazardous or sensitising products, e.g. monoclonal antibodies. When dedicated facilities are not available, a validated cleaning protocol between preparation of different classes of product should be developed and implemented. The use of closed system drug transfer devices to minimise cross-contamination should also be considered.

Occupational exposure to monoclonal antibodies, gene therapy and other biologically active substances may present a yet undisclosed risk of adverse effects to operators. Until definitive research proves otherwise, it is considered prudent to handle these substances in dedicated negative pressure (containment) clean areas to prevent exposure.

Materials containing live vectors and radio-pharmaceuticals **must** be handled in **separate** dedicated containment facilities.

Cleaning Premises for Aseptic Preparation

*PIC/S Guide (Annex 1, Section 2).*³ In addition:

- dedicated cleaning equipment should be used;
- cleaning should proceed from the cleanest area to the dirtiest area of the room. This would involve a ceiling to floor cleaning flow, moving outward from the ventilation to the exit;¹⁹
- an appropriate method of disposing of waste, including needles, should be established which does not allow accumulation in the area; and
- a cleaning log book should be maintained and include date of the clean, type of clean performed, type of cleaning agent used, name of operator/cleaner.

Routine Clean

- Cleaning, by the operator, of all interior surfaces of the LAFWS at the start and end of the work session or more frequently, depending on use.
- Using low-linting wipes and sterile 70% alcohol regularly throughout the work session. An alcoholic chlorhexidine solution may be used for the first and last cleans of the session. For salt and electrolyte residue, it may be necessary to dissolve the residue with sterile water before cleaning the workstation.
- Removing the sharps bin (when necessary).

Daily Clean

- Cleaning all equipment, exterior surfaces of the workstations, floor, basins and all other surfaces, knobs and switches.
- Mopping the floor, starting in the cleanroom and working out to the anteroom.
- Removing paper and contaminated waste containers.
- Removing the top sheet or cleaning of the adhesive mat.

Weekly Clean

All of the daily clean steps plus cleaning the walls and trolleys and equipment stands in the anteroom and cleanroom.

Monthly Clean

All of the weekly clean steps plus cleaning the ceilings.

Also refer to the Commonwealth Government's Infection control guidelines (Chapter 18).¹¹

OPERATOR VALIDATION

In addition to process validation outlined in the *PIC/S Guide (Annex 1, Section 4)* there should also be a documented system for operator validation.³

Operator validation should be used to assess the ability to maintain the sterility of materials during the preparation of aseptically prepared injectable dose forms. A system of operator validation should be used **prior** to undertaking aseptic preparation activities and for routine **ongoing** monitoring.

Operators need to demonstrate competency in aseptic techniques in order to prepare aseptic dosage units safely. A broth transfer test aids in this competency assessment, but in itself does not conclusively prove that operators can prepare aseptic dosage units accurately, precisely and safely. This can only be achieved by an objective assessment of an operator's routine aseptic technique and behaviour in a cleanroom.

One method of validation is the UK Universal Operator Broth Transfer Validation, which is designed to emulate some of the manipulations routinely used in aseptic preparation and handling activities.⁴⁶ The procedure will test the operator's ability to prevent microbial contamination of aseptic materials during a variety of reconstitution and transfer manipulations. Successful completion of this test by an operator indicates the achievement of an approved and transferable standard.⁴⁶

Handling microbial growth medium requires great care. Spills can result in contamination that may be distributed throughout the cleanroom suite. The ideal arrangement would be to locate a dedicated LAFWS in the Grade C zone, since (as demonstrated by van Doorne et al.⁴⁷) background air quality has little or no effect on the sterility of media transfers. This would also permit validation studies to be undertaken without interruption to daily production schedules and facilitates initial validation of new operators.

MONITORING

*PIC/S Guide (Annex 1, Section 6).*³ It is important that all staff on starting aseptic preparation ensure that all equipment is functioning satisfactorily. Potential problems should be reported to key personnel. Relevant records should be kept as defined in local procedures.

Environmental microbiological monitoring should be performed when the unit is in use. This may be achieved by exposing settle plates, performing finger dabs of gloves at the end of the work session, sampling surfaces with swabs or contact plates and active air sampling.

The Sterile Production Supervisor should assess all areas associated with aseptic preparation for compliance with the appropriate standards: on commissioning, following maintenance procedures, and routinely at an agreed frequency.

Particular importance should be attached to obtaining meaningful results, monitoring any trends and setting 'in-house' standards and action limits. Information should be actively and knowledgeably assessed and not merely filed for record purposes.

Each cleanroom unit should have a program of sessional, daily, weekly, monthly, quarterly or annual testing and re-certification of equipment that maintains the controlled environment to the appropriate standard with all results documented and retained for inspection. A recommended method is to chart results on a continuing basis so that trends are readily noticeable.

The optimum frequency for testing will depend on the unit and the activities undertaken, and on the requirements of relevant standards. However, monitoring is not a substitute for the continual vigilance of operators in ensuring the correct functioning of all equipment.

Testing and certification of the facility including the LAFWS and cytotoxic drug safety cabinets may be contracted to an accredited (e.g. National Association of Testing Authorities) external authority.

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