

SHPA Standards of Practice for the Safe Handling of Cytotoxic Drugs in Pharmacy Departments

SHPA Committee of Specialty Practice in Oncology

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

1. INTRODUCTION

This document is a set of guidelines, and cannot, nor does it claim, to cover every eventuality in the handling of cytotoxic drugs. Many cytotoxic drugs have been found to be mutagenic, teratogenic and carcinogenic on the basis of cell DNA, chromosomal studies, and, to a lesser degree, experience in treated patients.¹⁻¹⁵ The risk associated with occupational low-level exposure has not been determined. Therefore, without evidence to the contrary, risk is assumed to be present and proportional to exposure in a dose-dependent fashion.^{16,17}

Where the term cytotoxic drug is used within this document, it also applies to other hazardous drugs. Drugs considered hazardous include those that exhibit one, or more, of the following six characteristics in humans or animals: carcinogenicity, teratogenicity or other developmental toxicity, reproductive toxicity, organ toxicity at low doses, genotoxicity, and structure and toxicity profiles of new drugs which mimic existing drugs as determined hazardous by the above criteria.¹⁸ It is the responsibility of the pharmaceutical industry to provide information on investigational drugs which may be hazardous. This standard does not cover the handling of gene therapies.

Health workers preparing cytotoxic drugs without adequate precautions have been shown to contaminate themselves and their work environment.¹⁹⁻³¹ Reports of increased fetal loss and birth abnormalities in nurses, as well as anecdotal reports of other toxicities have been published.³²⁻³⁷ These reports relate to exposure occurring prior to the introduction of cytotoxic drug handling guidelines. The adoption of improved handling techniques and in particular the use of cytotoxic drug safety cabinets (CDSCs) has reduced exposure of cytotoxic drugs in health workers to levels that cannot be detected.^{21,28,38-42}

These standards should be read in conjunction with current SHPA guidelines for aseptic dispensing and standards of practice for the provision of clinical oncology pharmacy services.^{43,44} The Director of Pharmacy is responsible for ensuring the implementation of these standards within each institution.

2. OBJECTIVES

These standards have been prepared to describe the minimum requirements for the safe handling and preparation of cytotoxic drugs in pharmacy departments in terms of equipment, staff and documentation. It offers guidance to institutions for appropriate product preparation and operator safety, and should be considered the current national minimum accepted practice.

SHPA Committee of Specialty Practice in Oncology. **Jill Davis** (Chairman), **Stuart Harsley, Sue Kirska** (Convenor), **Robert McLauchlan, Li-ling Ng, Sheue-Ching Ooi, Angela Stefanou**

Address for correspondence: Ms Jill Davis, Pharmacy Department, Austin Health, PO Box 5555, Heidelberg Vic. 3084, Australia
E-mail: jillian.davis@austin.org.au

3. EXTENT AND OPERATION

Where an institution offers cytotoxic chemotherapy, all cytotoxic drugs used clinically must either be prepared by the pharmacy department in accordance with this standard or commercially sourced by the pharmacy.

Cytotoxic drugs must be prepared by pharmacy personnel (including after hours staff) who have undertaken appropriate training and validation in aseptic and cytotoxic drug reconstitution and handling techniques. Personnel must also have an understanding of the potential hazards associated with cytotoxic drug handling, and the special precautions required to prevent contamination of the operator, product and environment. Where available, specific courses should be used to train personnel involved in cytotoxic drug preparation.

4. POLICIES AND PROCEDURES

Precise operating and safety procedures for the handling of cytotoxic drugs and equipment must be established, documented and regularly reviewed.

4.1 Cytotoxic Cabinets and Pharmaceutical Isolators

Cytotoxic drugs may be prepared in either a CDSC or in a pharmaceutical isolator cabinet.

4.1.1 Cytotoxic Drug Safety Cabinets

CDSCs must comply with current Australian Standards.⁴⁵ Cabinets should be chosen with care to ensure that the safest and most operator friendly one is chosen. While the Australian Standards allow visual or audible alarms for indicating blower malfunction, audible alarms may startle operators and increase the risk of needle stick injury. Prior to 1994 the Australian Standards mandated the use of carbon filters to trap vaporised cytotoxic agents. In 1994 the use of the carbon filter was made optional. From 2002 the standard once again states that the use of a carbon filter is compulsory. If cabinets have been purchased since 1994, it should be ensured that they have carbon filters fitted.

4.1.2 Maintenance

CDSCs must be inspected and tested according to Australian Standards at least every 12 months and after relocation, mechanical or electrical maintenance.^{47,48} Not every test is considered compulsory by the National Association of Testing Authorities. Consideration should be given to more frequent testing when workloads are particularly high. The original copy of the test report must be retained in the pharmacy and be available to all staff members. A certificate summarising the test results should be attached to the cabinet. In case of cabinet failure, the cabinet must not be used until the fault has been rectified and the cabinet recertified.

4.1.3 Cleaning

CDSCs must be cleaned at the start and the end of each work session by wiping all internal surfaces with sterile

alcohol 70%. At the completion of each preparation, the cabinet floor should be wiped with sterile alcohol 70%. At the end of each day, the air intake grille should be lifted and the pre-filter surface inspected. If any items have fallen onto the surface of the pre-filter they must be carefully removed using forceps to ensure the pre-filter surface is not damaged. The sump area should also be cleaned with sterile alcohol 70%. At least weekly the internal surfaces of the cabinet should be cleaned with an appropriately diluted strong alkaline detergent, e.g. Decon-90. The cabinet must be carefully rinsed with sterile water to remove all detergent residues then finally wiped over with sterile alcohol 70%. The front glass barrier should only be lifted if the operator is wearing a suitable chemical respirator mask in addition to other protective clothing. A standard surgical mask provides insufficient protection for this procedure. Respiratory protection of a standard recommended in the current Australian Standards must be worn.⁵⁰

4.1.4 Isolator Cabinets

Isolator cabinets used for preparing cytotoxic drugs must comply with current Australian Standards.⁴⁶ Isolators must provide an equivalent level of protection to the operator, the environment, the product and service personnel as do laminar flow CDSCs properly installed in a sterile room. Isolator cabinets only offer full protection when they are in optimal working condition, therefore, a regular testing program must be instituted to ensure this is maintained. A recommended testing schedule is set out in the Australian Standard and includes daily glove tests, weekly leak tests and microbiological tests. Even though isolator cabinets are stand-alone units, they must be sited in a dedicated room used only for the isolator and its ancillary equipment.

4.2 Cytotoxic Cleanrooms and Anterooms

4.2.1 Standards

CDSCs must be housed in cytotoxic cleanrooms that comply with current Australian Standards.⁴⁷ Isolator cabinets are stand-alone units and must be sited in a dedicated room used only for the isolator and its ancillary equipment. It is highly recommended that this dedicated room be a cytotoxic cleanroom.

4.2.2 Design of Cleanrooms and Anterooms

Cleanrooms must be designed in accordance with Australian Standards.⁴⁸ The facility should be designed to allow easy and adequate access for personnel, equipment and cleaning.

The room surfaces and structure must be designed to minimise particle shedding and prevent the accumulation of particulate matter. The design must facilitate effective cleaning. Walls must be lined with a smooth, durable surface, lights recessed into the ceiling and the room should contain as few projecting ledges, shelves and extraneous materials as possible.

An effective airlock must exist between the cytotoxic suite and the external environment. Adequate procedures must be in place to prevent the simultaneous opening of doors and pass-through hatches. If interlocking doors are utilised, a safety override switch should be installed for emergency situations.

Appropriate hand washing facilities must be provided for personnel entering the cleanroom. Equipment which utilises an automatic hands-free operation system is recommended.

4.2.3 Ancillary Equipment

Equipment used in the cytotoxic cleanroom must be dedicated to the cytotoxic cleanroom only. Shelving used in the anteroom should allow the flow of air between shelves to minimise particle accumulation. Chairs or stools used in the cleanroom should be ergonomically designed and must not shed particles. Portable equipment such as trolleys are preferable to fixed shelving for the storage of consumables required.

4.2.4 Anterooms

The anteroom must be the only access to the cytotoxic cleanrooms, and should not share access to other non-cytotoxic cleanrooms. The anteroom should provide facilities for gowning of personnel entering the cleanroom. A mirror (preferably full length) must be made available in the anteroom so that staff can check that they are appropriately gowned prior to entering the cleanroom. Consideration should be given to the use of sticky mats.

4.2.5 Pass-through Hatches

A pass-through hatch is essential to prevent direct access between the cytotoxic cleanroom and the external environment. There are two possibilities for the location of pass-through hatches. Firstly, between the cytotoxic cleanroom and anteroom, and secondly, between the cytotoxic cleanroom and external environment. Should the latter be chosen, interlocking doors must be used and the unit must be hepafiltered and under negative pressure.

4.2.6 Communication

A hands-free communication system from the cleanroom to other rooms is required. Staff must not communicate through pass-through hatches or airlocks. Procedures must be in place to ensure any emergency communications are conveyed to personnel working in isolation in the cleanroom.

4.2.7 Monitoring

Manometers must be installed to give a continuous indication of the pressure differentials between the various rooms of the cytotoxic suite. A record of daily pressure differential readings must be maintained. Consideration should be given to the installation of manometer alarms, preferably visual, which alert staff to inadequate pressure differentials.

Microbiological testing and air particle sampling should be performed on a routine basis, and a log maintained of results.

The theoretic risk of cytotoxic contamination within the cleanroom exists. While overseas data is available,²⁵ these may not directly relate to Australian conditions due to differences in cabinet construction. If a practical method for detecting surface contamination were to become available in the future, this should be adopted.

4.2.8 Cleaning

The cleaning of the cytotoxic cleanroom and anteroom must be undertaken by personnel informed of the potential hazards associated with the handling of cytotoxic agents, and trained in the appropriate precautions to be taken. Cleaning must be in accordance with current Australian Standards.⁴⁷ Cleaning equipment used in the cytotoxic cleanroom must be dedicated to this purpose.

A written procedure for the cleaning of the cytotoxic cleanroom and anteroom must be prepared and maintained. All surfaces including the ceiling must be regularly cleaned. A cleaning log should be maintained.

Full protective clothing must be worn by cleaning personnel when inside the cleanroom. Protective clothing and recyclable cleaning equipment used in the process of cleaning must be treated as potentially contaminated and segregated and laundered separately.

4.2.9 Miscellaneous

Strict hygiene procedures must be developed and followed in the cytotoxic preparation suite. Eating, drinking, chewing gum and the application of cosmetics should be strictly prohibited.

Access to the cytotoxic preparation suite must be restricted to individuals working within the area. A sign restricting the access of unauthorised personnel should be prominently displayed.

Due consideration should be given to the availability of an emergency shower in close proximity to the cytotoxic preparation suite.

4.3 Drug Storage

Separate, clearly marked storage areas, including refrigeration, must be available for cytotoxic drugs. Cytotoxic drugs in storage must be clearly identifiable. All personnel involved in the receipt, distribution and storage of cytotoxic drugs must receive appropriate instruction on their hazards. An overseas study has shown cytotoxic contamination on the outside of cytotoxic vials.²⁹ It has been suggested that encasing glass vials in plastic can markedly reduce contamination. However, there is currently no data relating specifically to Australia. Consideration should therefore be given to wearing gloves whenever original packs of cytotoxic drugs are handled. Consideration should be given to preferentially purchasing products that are packaged in such a way to minimise the chance of breakage, e.g. plastic vials or plastic coated glass vials.

Facilities for the storage of cytotoxic drugs must be designed to prevent breakage and to limit the extent of contamination if leakage occurs. All personnel must be trained in the correct procedures to deal with any breakages and spills. Procedures for spills and emergencies, such as skin or eye contact, must be available to workers and prominently displayed in the area.

4.4 Personal Protective Equipment

Protective clothing must be worn by all personnel preparing cytotoxic drugs, cleaning cytotoxic preparation facilities, or cleaning cytotoxic spills. Personal protective equipment must not be worn outside the cytotoxic suite. Coveralls are preferable to gowns. Boots or overshoes, head covering, masks and gloves are also compulsory. Safety glasses are strongly recommended for wearers of contact lenses but are otherwise optional.

4.4.1 Coveralls

The most suitable types of coveralls are sterile, closed-front, long-sleeved with knit or elastic cuffs. These should be made from an impervious material.⁵¹ The cuffs should be tucked under the gloves. These may be disposable or can be processed through a laundry facility capable of handling garments contaminated with cytotoxic drugs.

Coveralls must be changed at least daily or if overt contamination results. Coveralls have a limited life span and must be discarded when full protection can no longer be guaranteed. Oversleeves can give added protection to the forearms (a vulnerable area of exposure).

4.4.2 Boots or Overshoes

The tops of boots or overshoes must be made from an impervious material and must be high enough to cover the trouser cuff if coveralls are used. The soles should be sturdy and made from a skid-resistant plastic.

4.4.3 Head Covering

Hooded coveralls are recommended. However, if using coveralls without hoods, caps must be worn to contain hair and reduce contamination. They should fit snugly around the head and in the case of a coverall, also around the face. Facial covers as outlined in the current Australian Standards must be worn by those people with beards or moustaches.⁵²

4.4.4 Masks

Masks that filter out aerosols as well as liquid spills are recommended. Standard surgical masks offer protection against the inhalation of powder, but not liquids and aerosols. Masks must be changed at regular intervals throughout the day. For cleaning spills outside of the CDSC a respirator mask complying with Australian Standards is recommended.⁵⁰

4.4.5 Gloves

The permeability of disposable gloves is inversely proportional to the glove thickness; the thicker the glove the less the permeability to cytotoxic drugs. A single pair of sterile purpose-manufactured gloves, two pairs of sterile surgical latex, or a pair each of polyvinyl chloride and sterile surgical latex gloves must be worn. Double gloving offers increased protection against the permeation of drugs.⁵³⁻⁵⁶ Gloves must be long enough to cover wrist cuffs of the coveralls while the arm is being bent or stretched. Powderless gloves are recommended. If powdered gloves are used, powder should be removed before entry into the cleanroom. Gloves must be changed at regular intervals, or whenever contamination is apparent or perforation occurs.

4.4.6 Safety Glasses

For maximal eye protection the use of safety glasses with side shields are recommended. If contact lenses are worn by the operator, safety glasses are strongly recommended.

4.5 Preparation

Standard operating procedures for the preparation of all cytotoxic drugs must be documented and followed to ensure operator safety, product sterility and environmental protection. Specific equipment for the preparation of cytotoxic drugs is necessary to limit the generation of aerosols and reduce the risk of environmental and personal contamination. Only specifically trained individuals must be allowed to prepare cytotoxic drugs.

Only one patient's treatment should be prepared at a time, and only one drug should be in the CDSC at any one time. Opened or used vials should not be left in the CDSC for later use.

4.5.1 Syringes

Luer lock syringes and fittings must be used in the preparation and administration of cytotoxic drugs to minimise the risk of separation of the connections. All cytotoxic drugs supplied as pre-filled syringes must have luer lock needleless closures attached. Luer slip syringes may be used for cytotoxic preparations only when luer lock connections are incompatible, e.g. intrathecal administration.

4.5.2 Needles

Wide bore needles (18 G/1.2 mm) are preferable when reconstituting and drawing up cytotoxic drugs to reduce the risk of high pressure syringing of cytotoxic solutions. The maximum recommended bore size for piercing additive ports is 21 G/0.8 mm. The use of filter needles (5 µm) is best avoided unless the drug has been removed from a glass ampoule or particulate matter is visible. If needles are recapped, it must be done in such a way as to minimise the risk of needlestick injury.

4.5.3 Syringe Tip Connectors

Syringe to syringe connectors must be used to maintain a closed system when transferring solutions from one syringe to another.

4.5.4 Hydrophobic Air Venting Devices

Techniques which avoid the generation of pressure differentials between the inside and outside of rubber-capped vials must be used. Air venting devices fitted with a 0.2 µm hydrophobic filter should be used to equalise pressures. Hydrophobic filters are not suitable for non-aqueous cytotoxic solutions. Negative pressure techniques may be used by operators trained and competent in this technique.

4.5.5 Glass Ampoules

Cytotoxic drugs presented in glass ampoules should be avoided whenever possible. To avoid injury or damage to gloves when glass ampoules are opened, either ampoule breakers or low-linting swabs should be used. Ampoules must be opened away from the operator. Filter needles (5 µm) must be used when dispensing cytotoxic drugs from glass ampoules.

4.5.6 Excess Drug and Air Containment

Appropriate steps must be taken to contain excess drug solution and air when priming syringes and other devices. Excess drug should be returned to the original container. In the case of drug removed from an ampoule, excess may be introduced into a closed container such as an empty sterile vial and discarded. Excess air may be expressed into closed containers or into the needle cap.

4.5.7 Extemporaneous Preparations

Extemporaneous preparations of cytotoxic drugs must be prepared under the same conditions as parenteral cytotoxic drug preparations.

4.5.7.1 Equipment

All equipment used in the preparation of cytotoxic drugs must be dedicated to this purpose and clearly labelled as such. This equipment must be cleaned immediately after use with a strong alkaline solution, with full protective clothing worn.

4.5.7.2 Mixtures

The crushing of cytotoxic tablets or opening of capsules in an open mortar should be avoided. For mixtures, many tablets may be dispersed in pre-calibrated bottles. Single dose mixtures are recommended.

4.5.8 Labelling

In addition to standard pharmacy labelling practices all containers of cytotoxic drugs should be labelled with a prominent warning. Nationally, cytotoxic materials are identified by a purple symbol representing a cell in late telophase. This warning should also be placed on the outer packaging of the product. The use of such labels on dispensed medication to patients taking the medication home is at the discretion of the pharmacist.

Drugs prepared for intrathecal use must be labelled both on the syringe and outer container with the warning 'For Intrathecal Use Only'. Departments must have strict procedures in place to ensure items intended for intrathecal administration are clearly identifiable and may be easily segregated from other preparations.

4.5.9 Packaging

Sealed, impervious containers should be used to package liquid cytotoxic drug preparations. This packaging may also offer protection from light. Drugs prepared for intrathecal use must be packaged separately.⁵⁷ When packaging for transport procedures outlined in another practice standard should be followed.⁵⁸

4.5.10 Tablets and Capsules

Tablets and capsules must be handled in a manner that avoids skin contact, liberation of powdered drug into the air and chemical cross-contamination with other drugs. All equipment used in the dispensing of cytotoxic solid dosage forms must be dedicated to this purpose and clearly labelled as such. Tablets or capsules must not be counted using a counting machine. Containers with damaged contents should be discarded.

4.6 Waste Management

Contaminated waste generated during the preparation of cytotoxic drugs and the cleaning of spills must be segregated, packaged and disposed off in a manner such that personnel and the environment are not contaminated. Relevant regulations concerning the disposal of cytotoxic waste must be followed.⁵⁹ Personnel involved in transporting cytotoxic waste must receive instruction on procedures for safe transport and for dealing with spills. Reference should be made to the relevant practice standard.⁵⁸

4.6.1 Preparation Waste

All cytotoxic waste must be placed in a closed system before removal from the cabinet. All sharps waste must be placed in puncture-resistant containers. All cytotoxic waste must be placed in secondary packaging and sealed to ensure that leakage cannot occur, and must be clearly labelled to indicate the presence of cytotoxic waste.

4.6.2 Transport

Procedures must be in place to ensure cytotoxic waste is collected, stored and removed from the facility appropriately. Cytotoxic waste must only be transported from the institution by approved operators familiar with emergency procedures to be followed in case of a spill.⁵⁸

8-24.6.3 Disposal

Cytotoxic waste must be incinerated in a facility approved by an environmental protection authority for the destruction of cytotoxic waste. Cytotoxic waste must not be mechanically compacted.⁵⁹

4.7 Cytotoxic Drug Spills

A standard operating procedure must be developed for handling cytotoxic spills in every institution. These spills may occur in the CDSC, the cleanroom, anteroom, the store, the pharmacy department, or during transport.

All personnel handling cytotoxic drugs must be given appropriate training in the procedures to be followed in event of a spill. Spill cleaning procedures should comply with Australian Standards.⁴⁷

4.7.1 Facilities and Equipment

4.7.1.1 Cytotoxic Drug Safety Cabinet

When a spill occurs within the CDSC, work should cease and the spill should be cleaned up immediately. Small spills may be easily and immediately cleaned up using absorbent gauze. Large spills, may require a spill pillow to absorb the greater volume of fluid involved. The area should be washed with an appropriately diluted strongly alkaline detergent solution (e.g. Decon-90), rinsed with sterile water and then wiped with sterile alcohol 70%.

4.7.1.2 Cytotoxic Cleanroom and Anteroom

Cytotoxic rooms which have a positive pressure in relation to the external environment should be fitted with a spill switch. This spill switch when activated alters the pressure differentials in the cytotoxic suite, thus minimising contamination of the external environment. Spill switches should be fitted with both a visual and an audible alarm and should be tested annually to ensure they are in good working order.

4.7.1.3 Store Room

All personnel working in the pharmacy store must be trained in the procedure to be followed in the event of both liquid and powder cytotoxic drug spills. Spill kits with written procedures must be available wherever cytotoxic drugs are stored (Section 4.3).

4.7.1.4 During Transport

Personnel transporting cytotoxic drugs from the pharmacy must be familiar with the procedure to be followed in the event of a spill.

4.7.2 Spill Register

A register of cytotoxic drug spills must be maintained indefinitely. All spills requiring the use of a spill kit or involving contamination of personnel, must be recorded in this spill register. Details of the day, date, drug, approximate volume, whether liquid or powder, and the name(s) of person/people involved must be documented in the register. Should the institution's incident report form include all of the above information, a copy of this form retained in the pharmacy is adequate.

4.7.3 Contamination of Personnel

In the event that personnel involved with a spill are contaminated, the following procedure should be followed:

- Overtly contaminated protective clothing must be removed and disposed of in the cytotoxic waste bin.

- All affected clothing should be removed, and if badly contaminated, discarded in the cytotoxic waste bin. Minimally contaminated clothing should be laundered separately and rinsed well.
- An emergency shower should be used if appropriate. Where this is not available, the contaminated area of skin must be washed with soap and flushed thoroughly with copious amounts of cold water.
- Eyes that become contaminated should undergo sustained irrigation with either a commercial eye irrigation solution or sodium chloride 0.9%. It is considered dangerous to irrigate the eye directly with running water from a tap due to the potential for water pressure damage.
- If skin is broken during the cleaning of a spill, the affected area must be irrigated with water, and bleeding controlled.
- Medical advice should be sought as soon as practical.
- An incident report should also be filled out if this is institution policy.

4.7.4 Contents of Spill Kit

A spill kit should contain:

- Instructions for use.
- Signs to isolate and identify the spill.
- Tyvek gown or coverall, boots, head cover, safety glasses with side shields, and toxic dust respirator mask.
- Two pairs of large gloves (to fit all).
- Plastic broom and dustpan to clean up broken glass.
- Spill mat (alginate impregnated) to absorb small volumes of liquid.
- Large quantities of swabs for absorbing and cleaning liquid spills.
- Concentrated alkaline detergent solution (e.g. 50 mL Decon-90).
- Water (for example, two 1 L bottles of water for irrigation).
- One clearly labelled cytotoxic waste bag.
- Spill Report Form (or institution incident report form).
- Spill pillow to absorb large volumes of liquid. May be integral part of spill kit or may be supplied separately when required.

All above contents may be supplied within a purple cytotoxic waste bin that then serves as the disposal receptacle.

4.7.5 Suggested Spill Clean-Up Procedure

In the event of a spill of cytotoxic material in any area other than inside the cytotoxic cabinet this procedure should be followed:

1. Secure and limit access to the area of the spill by placing the warning sign in a prominent position.
2. Remove the contents of the kit and put on in this order: the mask, head cover, safety glasses, one pair of gloves, (under cuff of gown) gown, boots and the other pair of gloves (over cuff of gown).
3. Carefully place sufficient swabs or alginate-impregnated mat (or a spill pillow if the spill is large) to cover the liquid spill. If the spill involves a powder, carefully place a mat over the powder ensuring minimal aerosol production, then carefully wet the mat to facilitate clean up.
4. Gather up the contaminated swabs/mat/pillow, and carefully collect any broken glass using the broom and dustpan provided. Discard everything including the broom and dustpan into the waste bag.

5. Continue steps 3 and 4 until the spill has all been cleared away.
6. Add the concentrated alkaline detergent (e.g. 50 mL Decon-90) to water for irrigation (e.g. 1L plastic bottle).
7. Wash the area of the spill thoroughly with spare towelling/swabs from the kit, discarding used material into the cytotoxic waste bag.
8. Rinse the area well with fresh water, again using spare towelling or swabs and discard into the waste bag.
9. Dry the area so as to prevent accidental slipping on the area if still wet.
10. Remove outer gloves and discard into the waste bag.
11. With the inner gloves still on, place the first bag inside the cytotoxic bin.
12. Remove boots, gown, safety glasses, head cover and mask in that order and discard into the cytotoxic waste bin. If not contaminated the safety glasses may be returned for future use along with any other unused materials.
13. Finally remove the second, inner pair of gloves and place in the cytotoxic waste bin.
14. Ensure all waste has been placed in the bin and arrange for collection as per standard institution policy.
15. Wash hands thoroughly with soap and water.
16. Arrange for hospital cleaning staff to re-clean the area.
17. Complete the spill report form and any institutional incident report form and arrange for a replacement spill kit.

4.8 Transport

Procedures for transporting cytotoxic drugs within the medical facility must be prepared and maintained.

Cytotoxic drugs must be packaged so as to provide adequate physical and chemical protection for the drug during storage and transportation, and allow for easy identification of the contained drugs. Drugs for intrathecal use should be transported separately from other cytotoxic dose forms.

Cytotoxic drugs for delivery within a medical facility should be sealed in plastic and placed in a hard-walled container appropriately labelled and dedicated for this purpose. The container must be made from moulded foam or other suitable packaging material capable of protecting the product from a shock equivalent to a drop of one metre on to a concrete surface.

All personnel involved in the delivery of cytotoxic drugs must be aware of the potential hazards and the care required in handling as well as the procedures to follow in the event of a spill. Cytotoxic drug spill kits must be readily available to personnel involved in the delivery of cytotoxic drugs.

For full details of requirements for transport of cytotoxic drugs from pharmacy departments refer to the relevant practice standards.⁵⁸

5. RESOURCES

Preparation of cytotoxic drugs must be carried out using equipment and facilities that comply with relevant Australian Standards.⁴³⁻⁴⁷ Facilities should include equipment capable of adequately labelling the products produced, identifying the product as cytotoxic and maintaining patient records which should be integrated with other pharmacy records. The facilities should be constructed such that there is adequate space and lighting so as to provide for a comfortable working environment. Glass walls or large glass windows should be included to provide external viewing. Rooms should be constructed to allow efficient workflow, allowing for

the assembly of drugs and equipment before preparation. An area should be provided within the facility to allow space for safe storage of cytotoxic drugs and other products and equipment requirements including an appropriately sized refrigerator and spill kits. Provision should be made for a workroom area in which paperwork and labelling can be done. This area should also contain an area for relevant references including easy access to the Internet. Reference materials on safe handling, drug preparation, and drug stability should be readily available in addition to procedure manuals and appropriate published literature regarding occupational exposure to cytotoxic drugs. Occupational Health and Safety is a responsibility of everyone within the institution and should follow any recommendations made at a state level. For example, see those published by Worksafe Victoria.⁶⁰ Appropriate occupational health and safety document including Material Safety Data Sheets should be stored in this area.

Institutions unable to provide all resources listed should outsource their cytotoxic products.

6. STAFFING AND STRUCTURE LEVELS

Sufficient allocation of staff must be made to provide for the expected workload in the cytotoxic preparation area. This staff allocation must be sufficient to allow for adequate breaks for those working in the cytotoxic cleanroom. It is recommended that no more than two hours be spent working at the cytotoxic cabinet without a break. That is, it is not acceptable to provide sufficient staffing based simply on the number of preparations made per week. Staffing should allow for the workload during the busiest periods and should take into account the complexity of products manufactured and not rely solely on the number of preparations made each week. If this is not possible, the outsourcing of some products must be considered.

Institutions offering cytotoxic chemotherapy must provide a clinical oncology pharmacy service that meets the requirements set out in the relevant practice standard.⁴⁴

6.1 Registered Pharmacists

A sufficient allocation of appropriately trained and validated pharmacists must be provided to oversee the production facility. A pharmacist must perform those functions requiring professional judgement in the manufacturing process and take final responsibility for the items produced.

6.2 Pre-Registration Pharmacists, Pharmacy Technicians and Assistants

Appropriately trained and validated support staff may be utilised in the manufacture of cytotoxic drugs under the close supervision of a registered pharmacist. A formal and stringent checking process with appropriate documentation must be in place for checking work done by non-pharmacists. A suggested checking procedure is outlined in Appendix 1. For reasons of safety, at no time should any more than two unregistered staff be supervised by one pharmacist.

6.3 Personnel Considerations

6.3.1 Exclusions from Working in Cytotoxic Preparation

6.3.1.1 Illness

Personnel with upper respiratory tract infections or cutaneous infections must be excluded from preparing

cytotoxic drugs whenever possible. Personnel taking immunosuppressive therapy should also be excluded.

6.3.1.2 Family Planning

Personnel who are pregnant or breastfeeding must be excluded from working with cytotoxic drugs.⁶¹ Personnel planning imminent parenthood must also be permitted exclusion from preparing cytotoxic drugs.

6.3.1.3 Abnormal Pathology Results

Personnel with abnormal pathology results should not prepare cytotoxic drugs until the abnormality has been investigated (Section 6.3.2.1).

6.3.2 Personnel Safety Monitoring

To reduce possible cytotoxic exposure, personnel must be adequately trained, and equipment must be functioning to appropriate standards. However, the literature contains many examples of reports that describe physical evidence of biological change following accidental and occupational exposure to cytotoxics. It is therefore prudent to have a policy in place for monitoring biological parameters of staff members who are involved in the preparation of cytotoxic drugs.

Policies developed for employees involved in the preparation of cytotoxic drugs should incorporate requirements of local and state government occupational health and safety, and workers compensation insurance requirements for employment medical examinations, and routine employee health monitoring.

6.3.2.1 Medical Examinations

There are no direct measurements to indicate total exposure to cytotoxic drugs.⁶²⁻⁶⁶ In view of this lack of data, non-specific measurements have been used as baseline and routine indicators. Arrangements must be made for appropriate explanation and counselling of staff with results outside the normal range. Anecdotally, blood tests have been used to identify personnel who should avoid exposure to cytotoxic drugs.²⁷ Personnel with results outside the normal range must be encouraged to have tests repeated, abnormalities investigated and should avoid preparing cytotoxic drugs until the significance of the abnormality is determined.

Pharmacists and support staff whose responsibilities involve parenteral cytotoxic drug manipulation should receive a baseline examination that includes assessment of indices such as full blood examination with white cell differential, and biochemistry (including liver function tests, urea, creatinine and electrolytes). These measurements may then be used to compare any subsequent measures taken either routinely or following accidental exposure.

Many tests have been developed which attempt to demonstrate low-level occupational exposure to cytotoxic agents. Currently there is no test that satisfies all the requirements for routine use, namely sensitivity, specificity, availability and cost. The usefulness of regular blood monitoring is doubtful because of the suspected long lag-time between exposure and effect observed on routine tests, and because of the difficulty in establishing a cause and effect relationship for abnormal results. However, until an acceptable routine test becomes available regular blood monitoring should be offered.

Regular monitoring which includes a full blood examination and differential, should be offered at a minimum of six-monthly intervals.

Institutions must have a written policy for baseline and regular monitoring of staff involved in the preparation of cytotoxic drugs.

Results of any medical examinations must be stored in their medical record.

6.3.2.2 Contamination of Personnel

In the event of overt contamination of personnel involving skin contact or skin penetration, tests performed under regular monitoring should be repeated. These tests should be performed immediately and medical advice sought. Full documentation of contamination of personnel must be recorded (Section 4.7.3).

7. TRAINING AND EDUCATION OF STAFF

All personnel must be trained in the safe handling of cytotoxic drugs and related wastes before working in the cytotoxic preparation facility. Training of staff in the manipulation of parenteral cytotoxic drugs should be undertaken by an experienced operator. This training must be structured and all stages must be documented. If an accredited training course is available it is recommended that personnel attend. Standard operating procedures for training should be developed and maintained. Each type of procedure to be undertaken in the CDSC should have a specific and detailed standard operating procedure. Before personnel attempt to prepare a preparation for a patient they must be trained in that particular standard operating procedure. If department resources do not permit such training, parenteral cytotoxics should be outsourced. Personnel must have passed both a validation of aseptic technique (e.g. using broth manipulations) and a validation in the preparation of parenteral cytotoxic drugs before being permitted to prepare cytotoxic drugs routinely. Revalidation should be undertaken every 12 months.

Personnel handling cytotoxic drugs should be provided with appropriate up-to-date information on all aspects of the safe handling of cytotoxic drugs, as well as the reported hazards of low-level exposure to these agents.

Recently it has been suggested that the outside of cytotoxic products arriving in pharmacy departments from suppliers may also be contaminated.²⁸ Consideration should therefore be given to the wearing of gloves when unpacking cytotoxic vials for passing into the sterile preparation area.

8. QUALITY

Quality assurance plays an integral part in providing a means for continually monitoring, assessing and improving the safe handling of cytotoxic drugs. Procedures must be reviewed on a regular basis and updated to reflect current guidelines for the safe handling of these drugs.

A program for continuing validation of aseptic technique and preparation of all cytotoxic drug products must be implemented and documented.

Microbiological testing and air particle sampling should be performed on a routine basis, and a log maintained of results.

The theoretical risk of cytotoxic contamination within the cleanroom exists. While overseas data is available,²⁵ these may not directly relate to Australian conditions due

to differences in cabinet construction. If a practical method for detecting surface contamination were to become available in the future, this should be adopted.

While end product testing is desirable, no practical implementation is currently available.

9. DOCUMENTATION

9.1 Procedural Manual

Each institution should make available to staff a manual that outlines the policies and procedures for the appropriate manufacture of cytotoxic drugs. The manual should include aspects of aseptic technique, cleaning procedures, cytotoxic drug spill cleaning procedures, transport procedures and health monitoring guidelines. Individual cytotoxic drug profiles outlining specific procedures for preparation should also be available.

9.2 Staff Training

Records should be maintained on staff training in validation of aseptic technique and preparation of cytotoxic drugs and spill management. These records should cover all personnel coming into contact with cytotoxic drugs, e.g. store personnel, cleaners and those involved in the transport of these agents.

9.3 Statistics

Each institution should keep statistics that outline the workload of the cytotoxic preparation suite. These statistics should reflect not only the quantity of items prepared, but include the complexity of workload.^{67,68}

9.4 Operator Log

A daily operator log must be maintained in perpetuity and should record the name and dose of products made, the operator's name and time spent in the cytotoxic cleanroom. This log must be available for both present and past employees. Documentation should include name, signature, drugs handled, date and time spent preparing cytotoxic drugs in the cytotoxic drug safety cabinet and details of other accidents or unusual events (e.g. failure of cabinet).

9.5 Contamination of Personnel Log

9.5.1 Spill Register

A log of personnel involved in spills must be maintained in perpetuity. Documentation should include name, signature, drugs spilled, date and time spent in the cleaning of spills. A brief description of how the spill occurred and suggestions on how to prevent future occurrences may be useful. It should also be noted if medical attention were sought. Should the institution's incident report form include all of the above information, a copy of this form retained in the pharmacy is adequate.

9.5.2 Accidental Contamination Log

A log of personnel involved in accidental contamination of personnel involving skin contact or skin penetration must be maintained in perpetuity. Full documentation of contamination of personnel must be recorded. Documentation should include name, signature, drugs spilled, date and time spent in the cleaning of spills. Reports of accidental contamination should be stored in the individual's employment record, and if contact with the skin or eyes, or a needlestick injury has occurred, the record of action taken and any treatment required should also be stored in the medical record.

9.6 Equipment Log

A CDSC log should be maintained which details events relating to the cabinet such as testing dates, filter replacements, cabinet relocations and breakdowns which can be used to establish a history of the cabinet's operating life. A manometer log should be used to record daily pressure differential readings. A microbiological testing log and air particle-sampling log should also be maintained.

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Appendix 1. Checking procedures for non-pharmacist staff

Non-pharmacist staff involved in cytotoxic drug preparation may include validated technicians or pre-registration pharmacists. Untrained technicians/assistants and pharmacy undergraduates should not be permitted to prepare cytotoxic drugs.

General points

Before preparation commences, all orders should undergo a full clinical check by the oncology pharmacist.⁴⁴ To minimise the potential for dosing error, vial sizes closest to the actual dose should be selected, e.g. for doxorubicin 70 mg, a 50 mg and a 20 mg vial should be used. Checks by a pharmacist should be made before components enter the cleanroom and when the product is finished. Volumes should be independently calculated by staff in the cleanroom. Each step of the checking procedure should be documented. Only one patient's treatment should be prepared at a time, and only one drug should be in the CDSC at any one time. Opened/used vials should not be left in the CDSC for later use.

Suggested checking procedure

Preparation set-up

After the components have been assembled, the pharmacist checks: correct drug and strength, dose-calculations, expiry dates, label details, reconstitution fluid, infusion bag, quantity of full vials and volumes of partial vials and signs that this check has been performed.

Finished product

The labelled, finished product is passed out with the completely and partially used vials. The completely used vials are sealed in plastic to avoid contaminating checking staff and the tops of partially used vials are foil sealed, marked with the date of opening and the volume remaining in the vial. If it has been necessary to withdraw fluid from an IV bag to make room for the drug, then the syringes of removed IV fluid are also passed out from the sterile room. The pharmacist checks the name and strength of the vials and diluents and IV fluids used, the number of full vials used, and estimates the volume remaining in the partial vial. For syringe products the volume is checked directly. For products in IV bags, if the amount of drug left over is within 10% of the volume expected, allowing for overage and inaccuracy in estimating volumes, then the product is deemed to be accurately prepared.

An institution may prefer to pass out used syringes drawn back to the volume of fluid used. If this procedure is followed, the syringes must be sealed in plastic before leaving the cleanroom to prevent contamination.

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