



Controlled environments

Part 5: Cytotoxic drug safety cabinets (CDSC)—Design, construction, installation, testing and use



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 - Australian Chamber of Commerce and Industry
 - Australian Industry Group
 - Australian Institute of Refrigeration Air Conditioning and Heating
 - CSIRO Australian Animal Health Laboratory
 - Engineers Australia
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 - International Society for Pharmaceutical Engineering
 - Office of the Gene Technology Regulator
 - Medical Technology Association of Australia
 - National Association of Testing Authorities Australia
 - NSW Ministry of Health
 - Society of Hospital Pharmacists of Australia
 - Therapeutic Goods Administration
-

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Australian Standard®

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Part 5: Cytotoxic drug safety cabinets (CDSC)—Design, construction, installation, testing and use

Originated as AS 2567—2002 and AS 2639—1994.
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PREFACE

This Standard was prepared by the Australian members of Joint Australia/New Zealand Standards Committee ME-060, Controlled Environments, to supersede AS 2567—2002, *Laminar flow cytotoxic drug safety cabinets*, and AS 2639—1994, *Laminar flow cytotoxic drug safety cabinets—Installation and use*.

After consultation with stakeholders in both countries, Standards Australia and Standards New Zealand decided to develop this Standard as an Australian Standard rather than an Australian/New Zealand Standard.

The objective of this Standard is to specify the basic requirements for cytotoxic drug safety cabinet (CDSC) design, construction, installation, testing and use.

A cytotoxic drug safety cabinet (CDSC) is designed to provide both an aseptic environment and containment of cytotoxic materials. However, in order to provide these conditions, the unit requires assistance from a network of specially designed cleanrooms. AS 2567 and AS 2639 are therefore being combined.

This Standard is Part 5 of the AS 2252 series on controlled environments. When the revisions of AS 2252.1—2002 and AS 4273—1999 (to be AS 2252.7) are completed, the series will comprise the following:

AS

- 2252 Controlled environments
- 2252.1 Part 1: Biological safety cabinets Class I—Design
- 2252.2 Part 2: Biological safety cabinets Class II—Design
- 2252.3 Part 3: Biological safety cabinets Class III—Design
- 2252.4 Part 4: Biological safety cabinets Class I and II—Installation and use (BS 5726:2005, MOD)
- 2252.5 Part 5: Cytotoxic drug safety cabinets—Design, construction, installation, testing and use (this Standard)
- 2252.6 Part 6: Clean workstations—Design, installation and use
- 2252.7 Part 7: Pharmaceutical isolators—Design, installation and use

Compliance with an Australian Standard does not of itself confer immunity from legal obligations.

The terms ‘normative’ and ‘informative’ have been used in this Standard to define the application of the appendix to which they apply. A ‘normative’ appendix is an integral part of a Standard, whereas an ‘informative’ appendix is only for information and guidance.

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FOREWORD

The use of cytotoxic drugs creates special problems in their preparation, manipulation and compounding. Many have been demonstrated to be mutagens and some to be carcinogens or teratogens in cell DNA and chromosomal studies, in animal models, and from experience with treated patients.

Some effects of exposure to these compounds may not manifest themselves for many years.

The aim of this Standard is to provide the following:

- (a) Protection of personnel and the immediate surrounding environment from aerosols, particles or vapours, which may be liberated in the preparation, manipulation, and compounding of hazardous products.
- (b) Protection of products so that they can be manipulated or compounded aseptically in a clean, controlled environment.
- (c) Protection of maintenance and testing personnel from exposure to toxic materials that may be found in cabinet filters and internal cabinet surfaces.

This Standard aims to provide mechanisms that form an integral part of an overall risk based approach that will provide a risk level that is as low as is reasonably achievable (ALARA) when cytotoxic materials are exposed within a CDSC.

As defined by AS 2252.1 and AS 2252.2, Class I and Class II biological safety cabinets are unsuitable for handling cytotoxic materials that are not inactivated by routine decontamination. In addition, Connor, T.H., Anderson, R.W., Sessink, P.J., Broadfield, L. and Power, L.A., 'Surface contamination with antineoplastic agents in six cancer treatment centres in Canada and the United States', *Am J Health Pharm*, July 1 1999, Vol. 56, No. 14, pp. 1427–1432, demonstrated that when cytotoxic drugs were compounded in Class II biological safety cabinets the exhaust HEPA filters alone did not totally arrest all cytotoxic drug residues released as aerosols within the work zone. Some drugs in regular clinical use, such as Cyclophosphamide, have the potential to sublime into the vapour phase, pass through the sump HEPA filter and potentially condense as solid drug films on surfaces within and surrounding the cabinet.

STANDARDS AUSTRALIA

Australian Standard Controlled environments

Part 5: Cytotoxic drug safety cabinets (CDSC)—Design, construction, installation, testing and use

1 SCOPE

This Standard specifies the basic requirements for cytotoxic drug safety cabinet (CDSC) design, construction, installation, testing and use. In addition, this Standard provides design requirements for the surrounding environment in which the CDSC is located and its installation.

2 APPLICATION

These are open-fronted safety cabinets which are primarily designed to be used with substances that are incapable of gaseous inactivation. The design of the CDSC provides greater protection to maintenance personnel than is possible with a Class II biological safety cabinet. CDSC design provides protection to the operator via an air barrier provided by an inward flow of air, protection to the product via a top-mounted fan and HEPA filter that provides clean, unidirectional air to the work zone of the cabinet and protection of maintenance personnel by a HEPA filter under the work zone that protects the cabinet internals from contamination.

A CDSC is designed to provide both an aseptic environment and containment of cytotoxic materials. It should be noted however that not all processes that occur within a CDSC are aseptic, such as work with prions (as specified in AS 2243.3) or other non-sterile processes where cytotoxic materials are potentially exposed.

NOTE: Appendix C deals with the use of CDSC with prions in microbiological containment laboratories.

Further to this, some processes will require regulation by local or national health authorities which may require additional testing, monitoring or enhanced design features.

Due to the broad range of processes and rapidly evolving technologies that incorporate a CDSC, this standard does not provide any guidance on any actual activity in a CDSC, with the exception of general housekeeping, cleaning, maintenance and spill management.

The superseded CDSC standards (AS 2567 and AS 2639) have mandated that the exhaust of the CDSC be passed through a carbon filter in order to capture any cytotoxic materials in a gaseous form. There is no doubt that some cytotoxic materials do volatilize, however, the level of risk that they can later condense on surfaces outside the cabinet, such as the room or exhaust ducting, cannot be determined. As a result the committee has decided that a carbon filter on the exhaust is still compulsory and is to be used in conjunction with a facility set up where the discharge of the cabinet is exhausted completely and immediately out of the room.

NOTES:

- 1 While providing protection from aerosols, a CDSC on its own is not capable of providing complete protection against gases and vapours that may be produced during compounding procedures. Gases produced by volatilized substances may be able to migrate through the cabinet HEPA filters and be discharged from the cabinet. Use of a CDSC with a carbon filter on its exhaust, operating in a cleanroom and discharging to a dedicated exhaust extraction system close to the cabinet is the most effective method to counter this problem.

- 2 Some operations that occur in a CDSC do not require an aseptic environment, therefore the room requirements are less critical. See Appendix C.
- 3 Where additional hazards occur, such as significant particle generation due to crushing or grinding of tablets, consideration should be given to using a Type 2 pharmaceutical isolator in accordance with AS 4273.
- 4 Appendix D has been included to provide assistance to users in purchasing CDSCs that will meet the requirements of this Australian Standard.

3 REFERENCED DOCUMENTS

The following documents are referred to in this Standard:

AS

- | | |
|---------|---|
| 1319 | Safety signs for the occupational environment |
| 1324 | Air filters for use in general ventilation and airconditioning |
| 1324.1 | Part 1: Application, performance and construction |
| 1324.2 | Part 2: Methods of test |
| 1668 | The use of ventilation and airconditioning in buildings |
| 1668.2 | Part 2: Mechanical ventilation in buildings |
| 1807 | Cleanrooms, workstations, safety cabinets and pharmaceutical isolators—Methods of test |
| 1807.1 | Method 1: Determination of air velocity and uniformity of air velocity in clean workstations, laminar flow safety cabinets and pharmaceutical isolators |
| 1807.5 | Method 5: Determination of work zone integrity |
| 1807.6 | Method 6: Determination of integrity of terminally-mounted HEPA filter installations |
| 1807.7 | Method 7: Determination of integrity of HEPA filter installations not terminally mounted |
| 1807.10 | Method 10: Determination of air pressure of cleanrooms and pharmaceutical isolators |
| 1807.15 | Method 15: Determination of illuminance |
| 1807.18 | Method 18: Determination of vibration in workstations, safety cabinets and pharmaceutical isolators |
| 1807.20 | Method 20: Determination of sound level at installed workstations, safety cabinets and pharmaceutical isolators |
| 1807.22 | Method 22: Determination of air barrier containment of laminar flow safety cabinets |
| 1807.23 | Method 23: Determination of intensity of radiation from germicidal ultraviolet lamps |
| 1807.26 | Method 26: Determination of air barrier containment of laminar flow safety cabinets—Potassium iodide discus test |
| 2013 | Cleanroom garments |
| 2013.1 | Part 1: Product requirements (this Standard is withdrawn, and has been included here for guidance only) |
| 2567 | Laminar flow cytotoxic drug safety cabinets |
| 2639 | Laminar flow cytotoxic drug safety cabinets—Installation and use |
| 4260 | High efficiency particulate air (HEPA) filters—Classification, construction and performance |
| 4273 | Design, installation and use of pharmaceutical isolators |
| 60529 | Degrees of protection provided by enclosures (IP Code) |

AS/NZS

- 2107 Acoustics—Recommended design sound levels and reverberation times for building interiors
- 2243 Safety in laboratories
- 2243.3 Part 3: Microbiological safety and containment
- 3000 Electrical installations (known as the Australian/New Zealand Wiring Rules)
- 3100 Approval and test specification—General requirements for electrical equipment
- 14644 Cleanrooms and associated controlled environments
- 14644.3 Part 3: Test methods (ISO 14644-3:2005, MOD)

AS/NZS ISO

- 14644 Cleanrooms and associated controlled environments
- 14644.1 Part 1: Classification of air cleanliness
- 31000 Risk management—Principles and guidelines

ISO

- 29463 High-efficiency filters and filter media for removing particles in air
- 29463-1 Part 1: Classification, performance testing and marking

EN

- 1822 High efficiency air filters (EPA, HEPA AND ULPA)
- 1822-1 Part 1: Classification, performance testing, marking

PIC/S

- PE 009 Guide to Good Manufacturing Practice for Medical Products

Connor, T.H., Anderson, R.W., Sessink, P.J., Broadfield, L. and Power, L.A., 'Surface contamination with antineoplastic agents in six cancer treatment centres in Canada and the United States', *Am J Health Pharm*, July 1 1999, Vol. 56, No. 14, pp. 1427–1432.

4 DEFINITIONS

For the purpose of this Standard, the definitions below apply.

4.1 Shall

Indicates that a statement is mandatory.

4.2 Should

Indicates a recommendation.

4.3 Unidirectional airflow

Controlled airflow through the entire cross-section of a cleanroom or a clean zone with a steady velocity and airstreams that are considered to be parallel.

NOTE: This type of airflow results in a directed transport of particles from the clean zone. Refer to AS/NZS 14644.3.

5 GENERAL REQUIREMENTS

5.1 Classification of physical containment

Four stages of physical containment are provided by the following barriers:

- (a) *Primary barriers* Provide immediate containment at the source. In this Standard, the cytotoxic drug safety cabinet is the primary barrier.
- (b) *Secondary barriers* Provide containment in the event of failure of the primary barrier or a spill outside the primary barrier.

NOTE: An example of a secondary barrier is the room (and its support facilities) within which the primary barrier is located.

- (c) *Tertiary barriers* Buildings in which the secondary barriers are housed.

NOTE: Consideration is to be given to the design or choice of the building, with due regard being given to the requirements of the secondary barrier and the intended processes.

Installations that provide a lesser degree of environmental and containment control than that specified in this Standard may not provide an adequate level of protection for personnel and drug products, regardless of the cabinet design.

- (d) *Quaternary barriers* Geographical sites for buildings constituting the tertiary barriers.

NOTE: An example of a quaternary barrier is an island.

5.2 Risk factors in assessing hazards

A documented risk assessment shall be undertaken to determine the level of physical containment that is required for safe operation of the CDSC. This involves an assessment of the potential hazards that may be encountered during the operation and maintenance of the facility.

NOTE: Examples of this type of data include a reference to the barrier requirements noted above. Greater detail is to be found in regional health guidelines for handling cytotoxic drugs. Guidance on risk assessments can be found in AS/NZS ISO 31000.

5.3 Primary barrier design

5.3.1 Work zone

The work zone is the internal space between the viewing window and air intake grille, the work floor and the protective guard below the supply HEPA filter.

5.3.2 Viewing window

The front of the cabinet shall include a viewing window extending the full width of the work zone to form a positive seal with the body of the cabinet in the working position. Materials selected for the viewing window shall be shatterproof and tested and proven to remain transparent and resistant to any change that would prevent clear visibility.

It shall be capable of being completely cleaned without removal.

The window should be vertically aligned with the front boundary of the unidirectional airflow outlet. Where a hinged window is used, a means shall be provided to secure the window in the closed position. Where a sliding window is used, means shall be provided to locate the window in the normal operating position. To facilitate cleaning and placement of equipment within the cabinet, means should be provided for holding the viewing window in the open position.

An audible or prominently visible alarm, which is activated when the window is other than in the fully-open or closed position, shall be fitted.

5.3.3 Air barrier and containment of hazardous material within the CDSC

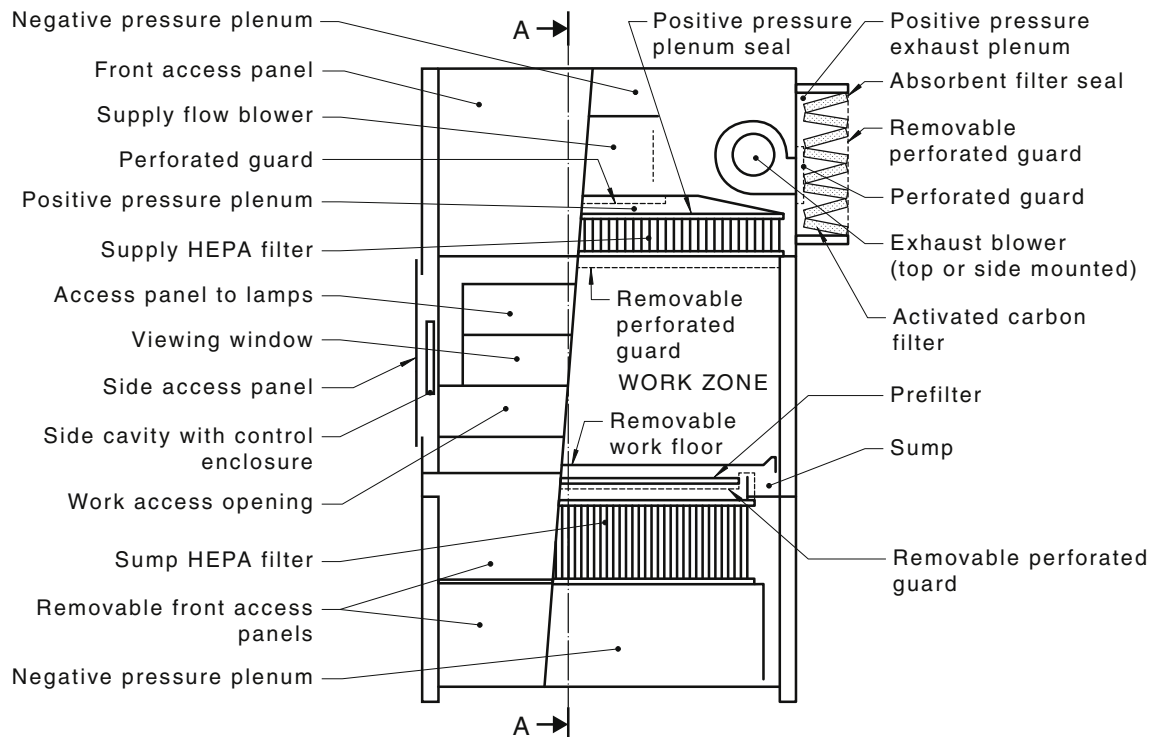
The design of the unit shall ensure that the integrity of the work zone is maintained so as to prevent entrainment of air from outside the unit.

An air barrier shall be created across the full width of the access opening by the induction of room air downwards through the air intake grille into the sump. This provides the primary barrier for the operator, product and surrounding environment. The combination of the air drawn into the cabinet from the outside and the air from the work zone shall pass beneath the work floor through the sump HEPA filter to the lower plenum, then via the return air plenum to the negative pressure plenum. A portion of the air at this point is exhausted out of the cabinet, to a volume that is equal to the air drawn in.

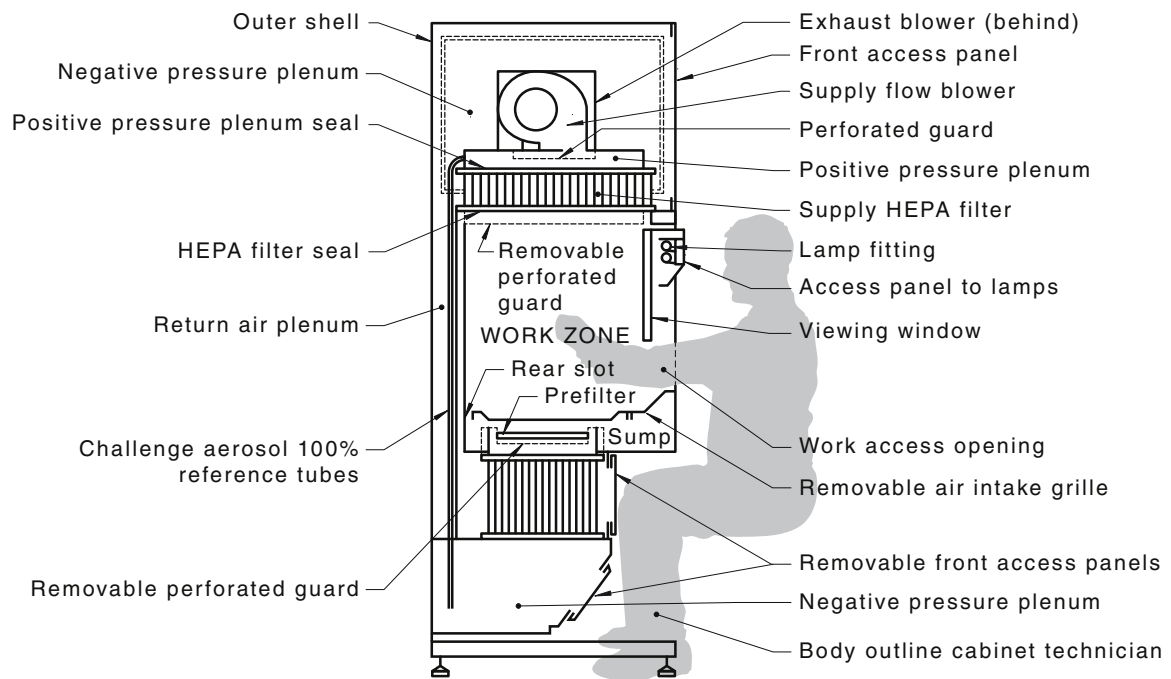
To enhance containment of hazardous materials within the cabinet, all potentially contaminated zones shall be under a negative air pressure relative to their immediate surroundings.

All filter seals, which may come into contact with potentially hazardous materials, shall be under a negative pressure in respect of non-contaminated zones, so that any air bypassing the filter seals flows inwards to the contaminated zones. The exception to this rule is the exhaust carbon filter and additional exhaust HEPA filter, if fitted, which will be sealed to the cabinet. In the event of failure of this seal the capture canopy will ensure removal of any bypass from the room. Regular testing as per Clause 8.6(e) will ensure that the carbon filter seal is integral. Any additional exhaust HEPA filters mounted on the cabinet shall be tested along with the rest of the HEPA filters as per Clause 7.2.1.

NOTE: For an example of a typical air flow arrangement for a CDSC, see Figure 1.



PART SECTIONAL FRONT VIEW



SECTION A-A

NOTE: Cabinet exhaust can be top or side mounted.

FIGURE 1 TYPICAL CYTOTOXIC DRUG SAFETY CABINET

5.3.4 Controls

All controls associated with the cabinet shall be integral parts of the cabinet and be accessible from outside the cabinet.

5.3.5 Design ergonomics and human factors

Ergonomics assists in the risk assessment of likely hazards associated with the physical, perceptual and cognitive demands when working with a CDSC. In order to make operating systems compatible with the needs, abilities and limitations of users, the risk assessment helps to identify the necessary modifications to design parameters of the equipment, standard operating procedures and the work environment in a specific facility.

General ergonomic considerations for users of a CDSC should include the following:

- (a) Work rosters—notably shift duration and frequency.
- (b) Position of operator, any notable static/long-term postures.
- (c) Fixed or adjustable chair/stool height.
- (d) Provision of a foot rest if required for a shorter operator.
- (e) Adequate work area space in relation to arm and body movement.
- (f) Forearm support without compromising the cabinet air barrier.
- (g) Adjacent bench space to avoid unnecessary material storage in CDSC.
- (h) Sight lines to equipment are clear.
- (i) Luminance at all work levels should avoid glare in the operator's eyes.
- (j) Noise reduction via acoustic analysis of enclosure and selection of room finishes.
- (k) Control of noise levels and heat emission from room activity.
- (l) Control of room temperature, humidity, air flow patterns and air velocity.
- (m) Safe access for routine maintenance and testing.
- (n) Provision for waste collection and disposal of hazardous materials.
- (o) Type of personal protective equipment (PPE) and whether gowns are disposable or require decontamination and cleanroom laundering.
- (p) Extent and type of data recording activity for communication system requirements within the work area using non-shedding technology.
- (q) Dealing with the potential of external contamination on containers of cytotoxic substances when handling outside the CDSC.

5.4 Secondary barrier design (Room)

5.4.1 Room requirements

The CDSC shall be located within a clean room that is serviced by an airlock, which may take the form of a change room. The clean room and the airlock shall maintain a pressure regime that will provide protection of the internal areas from outside contamination, and similarly, protection of the external environment from toxic materials that otherwise may escape from inside the room. See Section 8.

For operations that occur in a CDSC that do not require aseptic conditions, the room design requirements are less critical. Any variation to the room requirements shall be subject to a risk assessment. However, the cabinet design and testing requirements should still be followed.

NOTE: For prion work, see Appendix C.

5.4.2 *Treatment of CDSC and room exhaust*

Air discharged from the CDSC shall be exhausted completely from the room, through a HEPA filter mounted terminally to the ceiling surface (for a top-mounted exhaust) or wall surface (for a side-mounted exhaust). No direct connection of the CDSC to the external exhaust shall be made. A capture canopy shall be installed around the HEPA exhaust to assist with the entrainment of the CDSC discharge. See Figure 3.

6 CONSTRUCTION REQUIREMENTS FOR A CDSC

6.1 Outer shell

The outer shell shall be of metal, preferably stainless steel. If not of stainless steel, it shall be coated with a durable corrosion-resistant material and shall be sufficiently robust to prevent fracture or distortion in transport and installation. It shall also be easy to clean and resistant to decontamination.

6.2 Work zone

6.2.1 *General*

Except for the viewing window and the HEPA filter removable guard, the boundaries of the work zone, including the sump and the air intake grille, shall be constructed entirely of stainless steel. The grade of stainless steel used in the construction of the work zone should be selected for resistance to chemicals to be used during work procedures and in cleaning and disinfection. Grades 304 and 316 have been found to be suitable for most applications.

In order to prevent penetration by microorganisms, facilitate disinfection and prevent injury, all joints and surfaces in the work zone shall be finished smooth and crevice-free. Sealants shall be non-porous, with a smooth finish and resistant to chemicals and normal cleaning and disinfecting processes.

The HEPA filtered unidirectional airflow shall match the plan area and shape of the work zone as shown in Figure 2.