2002

Guide to Workstations for Cytotoxic Handling

Sewell, GJ

Hospital Pharmacy in Europe

Guide to workstations for cytotoxic handling

Workstations used by hospital pharmacists to reconstitute and compound cytotoxics must protect the infusion from microbiological contamination and the operator from the risk of occupational exposure

Graham Sewell
PhD BPharm MRPharmS
MRSC CChem MIBiol
CBiol

Professor
Department of
Pharmacy
University of Bath
UK

In many European countries the preparation of cytotoxic drug infusions for cancer chemotherapy has been centralised in hospital pharmacy departments, where expertise and specialised facilities are available to reduce the risk of contamination throughout the hospital. Pharmacists and pharmacy technicians responsible for centralised cytotoxic services have become increasingly concerned about the risks associated with occupational exposure to these drugs.[1]

The perspective of the regulatory authorities, such as the UK Medicines Control Agency, is mainly focused on protecting the patient from infusions contaminated with microorganisms.[2] Cytotoxic drug infusions can support microbial viability,[3] and inadvertent contamination could be particularly harmful to cancer patients who may be immunocompromised as a result of their treatment.

Two different workstation containment systems are widely used to protect both operators and infusions from cytotoxic and microbiological contamination, respectively.

Class II safety cabinets are made up of a modified vertical laminar flow cabinet with a large opening in the front fascia. This opening allows drugs and consumables to be moved in and out of the cabinet work area, and also provides access for the operator's arms to carry out the necessary manipulations in the cabinet. The high-efficiency particulate air (HEPA)-filtered laminar airflow protects the infusion from ingress of microorganisms and particles, and the operator is protected by an air curtain that is channelled over the face of the opening into a grill located on the front edge of the work area (see Figure 1).

Isolators (also known as class III cabinets) are fully enclosed systems of either rigid or flexible film construction. HEPA-filtered air, either turbulent or laminar flow, is supplied to the main work area, and materials are transferred in and out of the isolator through transfer hatches that are also flushed with HEPA-filtered air. The operator gains access through sleeve and glove arrangements (usually two or four per isolator), which maintain the integrity of the isolator (see Figure 2). Isolator work areas are designed to operate at either positive pressure (type I isolator) or negative pressure (type II isolator). For cytotoxic handling, negative-pressure operation is generally favoured because in the event of a leak developing cytotoxic drugs will still be contained within the isolator.

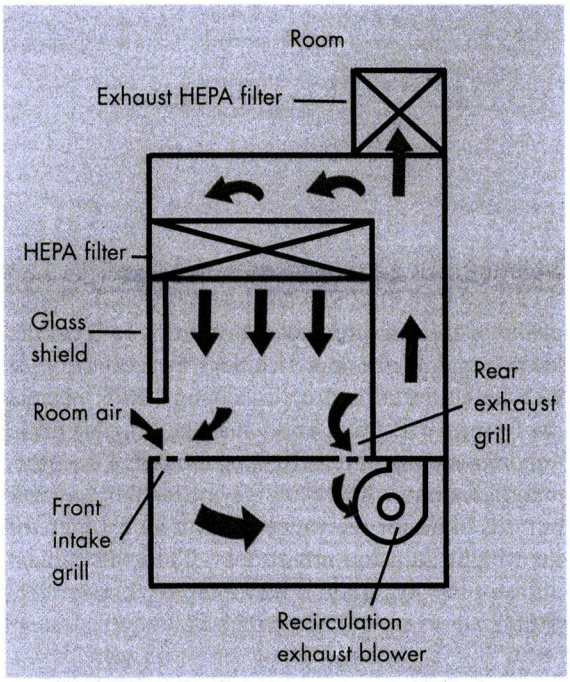

Figure 1. A Class II safety cabinet
Filtered laminar airflow protects the infusion from contamination by microorganisms and particles

Design standards

In terms of product protection, both class II safety cabinets and isolators are designed to achieve an EC Good Manufacturing Practice (GMP) Class A environment in the controlled workspace.[4]

There is no European Standard for class II safety cabinets, but there is an Australian Standard.[5] This requires that all potentially contaminated parts,

Figure 2. A sleeve and glove arrangement
Used to handle drugs within an isolator or class III cabinet

including filter seals, are maintained at negative pressure with respect to uncontaminated areas, and that exhaust air passes through a carbon filter in addition to a HEPA filter.

There are no official standards for isolators, although these may be included in a new standard for cleanrooms under development by the International Organisation for Standardisation Technical Committee ISO/TC209. A document published in the UK does outline design principles and operational procedures for negative-pressure isolators intended for handling cytotoxic drugs.[6]

Most isolators designed for cytotoxic use are of rigid construction, with either turbulent or laminar air-flow creating typically 1,500–3,500 air changes per hour in the workspace and 200–400 air changes per hour in the transfer hatch devices. Transfer hatch doors are interlocked and fitted with a time delay (typically preset to two minutes). This precludes direct contact of the controlled workspace with the outside environment and ensures that there is adequate contact time between surface sanitising agents and drug vials or consumables before they are introduced into the controlled workspace.

Operational characteristics

One of the key factors leading to the introduction of isolators into hospital pharmacy practice during the 1980s was the (erroneous) perception that isolators could be located in a "socially clean" area rather than a cleanroom. It is now recognised that both isolators and class II safety cabinets must be located in a cleanroom.[7] Depending on the type of transfer device used, an isolator may be located in a minimum EC GMP Class D environment, whereas a class II safety cabinet requires EC GMP Class B.[8]

Unlike class II safety cabinets, isolators have no front aperture for the introduction and removal of materials from the controlled workspace. Although the surface sanitisation of materials and consumables is identical, the transfer of materials in and out of isolators is a more complex multistage process, and access for cleaning of the work area can be more difficult in some cases.

The other main difference is the sleeve-glove arrangement used in isolators for manipulation of cytotoxic infusions in the workspace. Specially designed cuffs at the end of isolator sleeves allow experienced operators to change gloves without compromising the Class A environment. These differences require additional training before an operator is competent in the safe use of isolator technology. Photographs illustrating the key differences between class II cabinets and isolators are shown in Figure 3.

Monitoring and process validation

Isolators are fitted with pressure gauges for continuous monitoring of controlled workspace and transfer hatch pressures. These are supplemented with audible and visual alarms, together with systems to measure pressure differentials across HEPA filters for detection of blockages and breaches of integrity. Gloves and sleeves must be inspected visually at each work session for holes and tears, and the integrity of the complete glove-sleeve system is determined on a daily basis using specialised pressure monitoring apparatus. The integrity of the isolator as a whole is checked on a weekly basis using pressure decay tests specified by isolator manufacturers or those described in the publication *Isolators for pharmaceutical applications*.[6]

Class II safety cabinets also permit continuous monitoring of pressure in the workspace and across HEPA filters. An operator protection test (KI discus test to European Standard BSEN 12469:2000) is conducted on a yearly basis to assess effectiveness of hazard containment. This standard requires a protection factor $>1\times10^5$. However, air turbulence in front of the aperture caused by operator movement or airflow in the cleanroom can cause a correctly functioning cabinet to fail this test.

Further monitoring common to both isolators and class II cabinets would include airflow measurements, subvisual particulate counts, and a range of microbiological tests including active sampling, settle plates, surface swabs and finger-dab plates. Product protection is validated using broth-transfer simulations. These tests are described in detail elsewhere.[8]

Which is best?

Intuitively, the product and operator protection offered by isolators would seem to be superior because these systems are totally enclosed. There is no published evidence to support this view, although a North American multicentre study did find significant

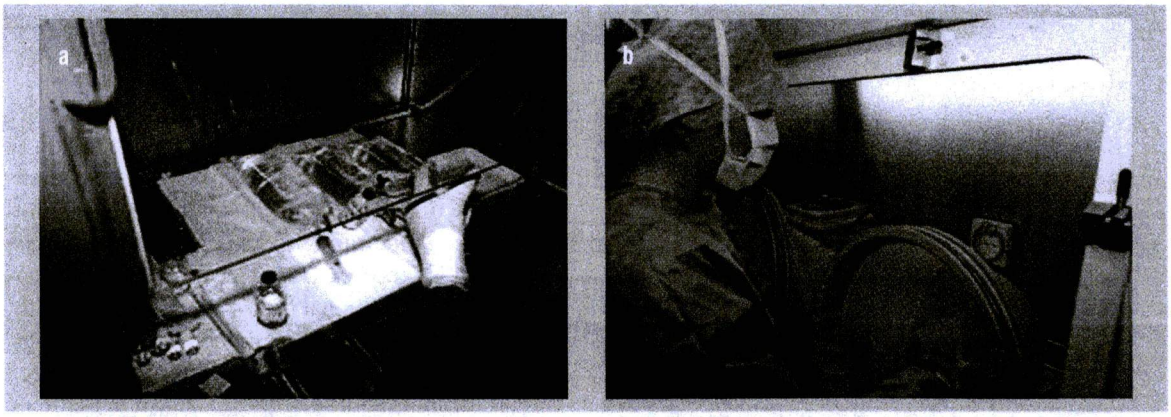

Figure 3. Workstations for cytotoxic handling
a. Class II safety cabinet. b. Isolator

cytotoxic contamination in the vicinity of class II safety cabinets.[9] The main weakness of class II cabinets is the front aperture, although small pinholes in gloves and sleeves are a potential problem with isolators. Initially, operators may find isolators more difficult from an ergonomic perspective, although this usually diminishes with experience. Also, the cost of isolators is approximately twice that of class II cabinets.

Recent studies have demonstrated vaporisation of cytotoxic drugs at room temperature.[10] Cytotoxic vapour would not be retained by HEPA filters and may permeate carbon filters, so cabinets and isolators recirculating air back into the cleanroom may cause contamination. Therefore it is preferable to externally duct exhaust air from these devices.

New developments

The introduction of gas-sterilised isolators, where the isolator workzone and a single-batch load of components and consumables are sterilised by a gas (eg, peracetic acid), may offer a solution to the questionable effectiveness of surface sanitisation of components.[11]

In the UK, regulatory bodies are debating the operating pressure of isolators used for cytotoxics. The Health and Safety Executive favours negative pressure (protection of operator), while the Medicines Control Agency advocates positive pressure (protection of product). A final report has yet to be issued, although it appears that either type of device may be acceptable providing the isolator is located in an appropriate environment and integrity tests are conducted routinely.

Finally, with the issues of cytotoxic vaporisation and the emergence of new gene therapy products, there is concern over the risk of drug cross-contamination in isolators and class II cabinets. The use of a new solution-transfer device, which remains fully enclosed while balancing air pressure as liquid is added to and removed from drug vials, may prevent contamination of the controlled workspace.[12] ■

References

1. Clark C. Occupational exposure to cytotoxic drugs. *Pharm J* 1999;263:65-7.
2. Needle R, Sewell GJ, Summerhayes M. Current issues in centralised additive Services. *Hosp Pharmacist* 1998;5:103-4.
3. Kramer I. Viability of microorganisms in novel antineoplastic and antiviral drug solutions. *J Oncol Pharm Pract* 1998;4:32-7.
4. European Commission. *Good manufacturing practice for medicinal products.* Volume IV. Brussels: European Commission; 1992.
5. Anon. *Cytotoxic drug safety cabinets.* AS 2567. Sydney: Standards Association of Australia; 1982.
6. Lee MG, Midcalf B. *Isolators for pharmaceutical applications.* London: HMSO; 1994.
7. Sewell GJ. Experience with isolators in the UK – the first 10 years. *Swiss Pharma* 1998;5:S29-33.
8. Beaney AM, editor. *Quality assurance of aseptic preparation services.* 3rd edition. London: Pharmaceutical Press; 2001.
9. Connor TH, Anderson RW, Sessink PJ, et al. Surface contamination with antineoplastic agents in six cancer treatment centres in Canada and the United States. *Am J Health-Syst Pharm* 1999;56:1427-32.
10. Kiffmeyer TK, Kube C, Opiolka S, et al. Vapour pressures, evaporation behaviour and airborne concentrations of hazardous drugs: implications for occupational safety. *Pharm J* 2002;268:331-7.
11. Wastnage RJ, Lowe C, Davies C, et al. New aseptic suite at Singleton Hospital. *Hosp Pharmacist* 1998;5:70-2.
12. Vandenbroucke J, Robays H. How to protect environment and employees against cytotoxic agents , the UZ Ghent experience. *J Oncol Pharm Pract* 2001;6(4):146-52.