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The use of isolators for cytotoxic drug handling in hospital pharmacies

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Many issues relating to isolator use in hospital pharmacies are under debate, including the quality of the background environment, sanitisation of materials transferred into isolators, the use of positive or negative pressure isolators for cytotoxics, ergonomics and gaseous sterilisation. However, continuing improvement in isolator design, isolator monitoring and the understanding of isolator technology means that the use of these devices is now well established in the UK and is becoming increasingly widespread throughout mainland Europe.

Isolators were introduced into hospital pharmacy practice in the late 1980s, and initially the technology was slow to gain acceptance. Pharmacy technicians found isolators uncomfortable to work with, and the glove/gauntlet systems available at the time were constructed of thick latex which caused loss of feel and manual dexterity during manipulative operations.

Pharmacists managing centralised IV additive services (CIVAS) were unsure of the technology employed, and most CIVAS units continued with conventional cleanrooms, using laminar air flow workstations for non-hazardous medicines and class II safety cabinets for handling cytotoxic drugs.

By the end of the decade a combination of factors resulted in the more widespread adoption of isolator technology. The loss of Crown immunity in 1990 and the subsequent requirement for hospital pharmacy production units to obtain manufacturers' 'specials' licences raised the standard of hospital facilities. However, severe cash shortages in the UK health service often precluded the refurbishment of conventional cleanrooms.

In any case, it was thought at the time that isolators could be operated in any 'socially-clean' background environment[1] and isolators were being promoted as a low-cost alternative to cleanrooms. However, as hospital pharmacists increased their understanding of the limitations and quality assurance issues relating to isolator technology, the absolute necessity for a cleanroom background environment became obvious.

Today, the cost-saving argument can no longer be sustained, and the main function of isolators in current hospital practice is the containment of hazardous materials such as cytotoxic drugs, while maintaining a high-quality aseptic work zone.

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Isolator construction

Isolators provide a totally enclosed work area with high-efficiency particulate air (HEPA)-filtration air, enabling the controlled work zone to reach European Community Good Manufacturing Practice (EC GMP) class A standard.[2] Isolators may be of a flexible or rigid structure.

Flexible isolators are constructed from a PVC film, supported by a framework which is usually made of stainless steel. For cytotoxic work, isolators are normally operated under negative pressure with respect to the outside of the isolator; in the case of flexible film isolators, an extensive framework structure is required to prevent the PVC film collapsing on itself.

HEPA-filtered air is usually introduced from above the work area and the terminal HEPA input filter normally runs the full length of the work area. The air input may be of either laminar or turbulent flow pattern, with the former as the preferred option.

Materials are passed to and from the controlled work zone via transfer devices. In most cases these are of rigid construction and are supplied with HEPA-filtered air, either by exhaust from the controlled zone or from an independent supply.

Interlocked doors provide access to (a) the transfer device and subsequently to (b), the controlled work zone. In some cases the transfer device may facilitate docking to a capsule which contains pre-sterilised components, or to another isolator. Whatever type of transfer device is used, the pressure is controlled to a more negative value than the work zone to prevent the ingress of potentially non-sterile air into the critical area.

Manipulation inside the work area is facilitated by

glove ports, usually two or four per isolator, depending on whether the equipment is designed for use by one or two operators. Most isolators now use a flexible sleeve made from a bi-layer of PVC with dacron liner attached to a cuff-ring.

Gloves, usually of latex or nitrile construction, are then attached to the end of the cuff-ring. This type of arrangement enables gloves to be changed on a regular basis in a manner which does not breach the integrity of the isolator. A typical glove and sleeve arrangement is shown in **Illustration 1**.

Gloves used with isolators should be designed for

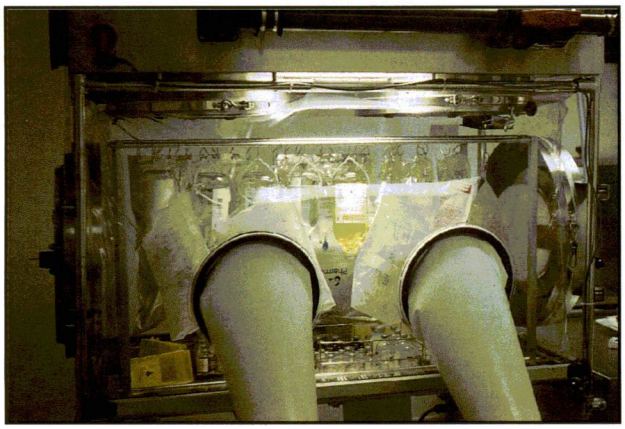

Illustration 1: Isplator sleeve, cuff and glove arrangement

cytotoxic handling, or at least should conform to BS 400S[3]. In large flexible film isolators the glove ports are replaced by a half-suit arrangement which allows the operator to 'work' centrally in the critical zone.

For cytotoxic work, rigid isolators are more common. The cabinet is of rigid construction with a rigid plastic viewing window at the front. The transfer device and glove-port arrangements are similar to the flexible film devices.

Rigid isolators are less prone to pinhole leaks than their flexible counterparts, but the integrity of seals between panels is critical to prevent ingress of air from the outside. A schematic diagram of a typical rigid isolator in widespread use for cytotoxic reconstitution is shown in the **Figure**.

Modern isolators are equipped with comprehensive alarm and warning systems. These indicate power failure, variation in air flow to work area or transfer devices that are outside preset limits, and variation in pressure (due to loss of cabinet or glove integrity, for example). Alarms also indicate when input or exhaust HEPA filters are blocked and require changing.

Most isolators are fitted with manometer or magnahelic gauges to the main work area and transfer hatches, to monitor pressure. Also, the interlocked transfer hatch doors are often controlled by a time-delay which is set to a previously validated value, usually two to five minutes. This ensures that surface sanitisation agents, such as 70 per cent industrial methylated spirit, have time to exert a bactericidal effect before materials are transferred into the critical zone.

Negative pressure or type II isolators for cytotoxic

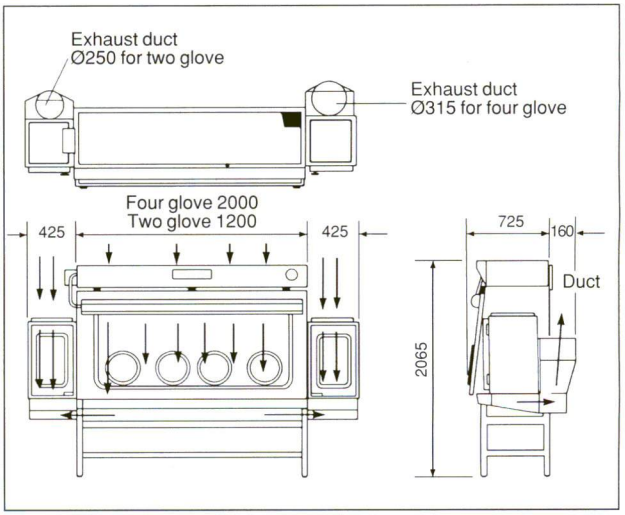

Figure: Schematic diagram of Medical Air Technology four-glove isolator, showing air-flow pathways

work may either recirculate exhaust air from the isolator back into the room via a double HEPA filter or, alternatively, exhaust via a single HEPA filter to an external duct located at high level.

From a health and safety viewpoint, external ducting is preferable but the air input into the cleanroom must be sufficient to compensate for the additional air extracted via the isolator. If gases such as formaldehyde or peracetic acid are used to sterilise isolators then external ducting is essential. **Illustration 2** shows externally-ducted negative pressure isolators located in a cleanroom.

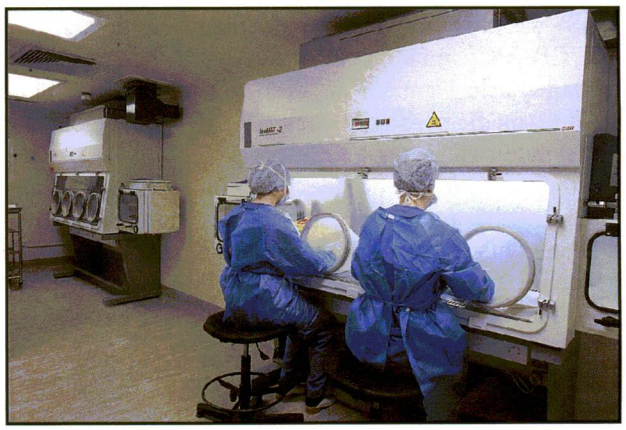

Illustration 2: Externally-ducted negative pressure isolators

Standards for isolators

Although there are no official standards for isolators in the UK, there are several documents which provide guidelines on the construction, use and monitoring of isolators. The most significant, *Isolators for Pharmaceutical Applications*[4], provides guidance for both manufacturers and users of isolators.

The guidance document, *Aseptic Dispensing for NHS Patients*[5], was published in 1994 following the so-called Manchester incident in which two children died as a result of microbiological contamination in

parenteral nutrition fluid prepared in a positive pressure isolator.[6] Although the isolator was not implicated in the cause of this tragedy the guidance document directed that 'the principles of operation for isolators should be the same as for cleanrooms'.[6]

The Rules and Guidance for Pharmaceutical Manufacturers and Distributors[7], published in 1997, highlighted the need for validation of isolators and made recommendations on suitable background environments for the siting of isolators. Specific guidance on validation and monitoring of isolators has been published by the UK Regional QC (quality control) subcommittee.[8] (Incidentally, although the regional basis to the health service has now gone, this nationally-drawn committee remains.)

These aspects are considered in more detail later in this article.

The validation of isolator technology for aseptic processing of cytotoxic drugs can be broken down into three components: equipment, operator and process validation.

Equipment validation

Initial commissioning, validation and regular revalidation are essential, to ensure that isolator performance reaches and maintains the required specification for cytotoxic reconstitution. In essence, this means compliance with guidelines relating to the aseptic preparation environment[4, 5, 7, 8] and maintaining effective containment of the cytotoxic hazard.

It is also important to recognise that the performance of isolator equipment is dependent on the background environment in which the isolator is located. Validation must therefore be carried out with the isolator installed in the site where it will be operated.

Validation should include all the isolator systems, and cover the integrity of the isolator casing, gloves and sleeves, the air flow and air velocity, pressure differentials, alarm systems, the function and integrity of HEPA filters, pressure gauge calibration and the operation of transfer hatch interlock devices. Guidance on microbiological, physical and integrity tests for isolator validation is provided in the appendices of Isolators for Pharmaceutical Applications.[4]

Operator validation

Operators unfamiliar with isolators must be validated before they are permitted to prepare medicines for patient use in isolator workstations.

Operator validation would typically include hand washing, changing into cleanroom clothing, and changing isolator gloves. Local procedures using contact plates or sterile swabs would be drawn up for this work. New operators, and experienced operators undergoing revalidation, would be expected to complete a series of broth-fill exercises without microbial growth.

Validation of safe handling and avoidance of chemical cross-contamination is achieved through the manipulation of sterile solutions in which the drug is replaced by a fluorescent dye (quinine sulphate, for instance). The work area inside the isolator and the operators' gloves are then scanned with a portable ultraviolet (UV) lamp which reveals contaminated surfaces by visible fluorescence.

Competency assessment programmes are used to validate operators' grasp of the theory and practice of aseptic techniques using isolators; operators are assessed by observers, and all competency assessments are fully documented.

Process validation

Broth fills are the mainstay of process validation in isolators. The broth fill should replicate as closely as possible actual reconstitution and filling processes. If a range of different devices is filled (such as syringes, minibags, infusion devices), then they should be included in broth fills by rotation. Clearly, broth fills also simultaneously validate equipment and operators in addition to the process.

The processes of vial/component transfer into the isolator, and cleaning of the isolator, also require validation. In the case of the former, a series of vials or components is sanitised in accordance with standard operating procedures (SOPs) and transferred into the isolator. The microbial contamination on the surface of vials or components is then assessed, using contact plates or by immersion in sterile broth.

The cleaning of isolators is validated in order to avoid cross-contamination. This is achieved by deliberate contamination of the isolator work area with a solution of quinine sulphate, and visualisation of fluorescent areas with a UV lamp before and after the cleaning process.

Isolator operation

The operation and use of isolators must be controlled by the implementation of SOPs. These procedures must be approved by the individuals responsible for production and quality assurance and, where appropriate, the procedures must be fully validated (cleaning, for example).

In many large hospital pharmacy departments the cytotoxic preparation work, such as batch preparation of prefilled syringes, will be carried out under a Specials Manufacturing Licence and also under Section 10 of the Exemption of the Medicines Act (in the case of named-patient medication, for instance). The SOPs for isolator use must therefore incorporate the guidelines and practice recommendations in guidance documents relating to both systems.

These are the *Rules and Guidance for Manufacturers and Distributors 1997*[7], *Isolators for Pharmaceutical Applications*[4], *Aseptic Dispensing for NHS Patients*[5], and the Regional QC Pharmacists' document on the *Quality Assurance of Aseptic Preparation Services*[8]. Useful practical guidelines on isolator operation are provided in the *Cytotoxics Handbook*.[9]

Typically, SOPs will cover operator hand washing and gowning, isolator cleaning before and after use, inspection of isolator, gloves and sleeves before use, sanitisation of components and consumables, segregation of batches, introduction and removal of components into and out of the isolator, glove changing, product processing and emergency procedures (the response to power failure, for example).

Workload capacity planning is essential to ensure that the isolator workspace and operators can adequately handle the demands placed on them. The SOPs should reflect this and limit both the maximum batch size and the daily workload to previously agreed levels.

In view of the potential occupational health risks associated with handling cytotoxic drugs, it is essential that all procedures comply with the UK Control of Substances Hazardous to Health Regulations 1988.[10] It has been recognised that methods to determine environmental contamination by cytotoxics and occupational exposure to cytotoxics lack the sensitivity, precision and prognostic significance to be of value.[11] Efforts should therefore be focused on hazard containment and safe working practices.[11]

In practical terms, this involves testing the integrity of the isolator and the efficiency of isolator-exhaust HEPA filters, and using protective gowns and gloves specifically designed for the protection of operators handling cytotoxic drugs.

The ergonomics of isolator operation should also be considered, and a recent report has identified many of the factors which influence operator comfort and efficiency during aseptic manipulation work.[12] These issues should be addressed through careful isolator and cleanroom design, the use of adjustable cleanroom chairs, workload and capacity planning, and the preparation of work rosters to ensure that individual operators are not working in isolator workstations for excessive periods.

Monitoring of isolators

As with conventional laminar flow cabinets, routine monitoring of isolators is essential.

However, access to the controlled work zone of isolators can be difficult for some monitoring procedures, such as active microbiological sampling. Unless the isolator is fitted with sampling ports, or equipment can enter the work zone via transfer hatches, it may be necessary to puncture isolator gloves to permit the introduction of sampling probes for monitoring purposes. The need for routine monitoring must therefore be balanced by the potential risk of compromising isolator integrity and the ingress of contamination.

The type and frequency of monitoring required is detailed in the literature.[4, 8] A schedule of monitoring currently acceptable to the UK's Medicines Control Agency (MCA) is presented in the **Table**.

Table: Monitoring programme for isolators

Frequency	Test		Limits	
Each work session	Finger dab plates (2 per operator)		1 colony/plate	
	Settle plates	(a) work zone	1 colony/2 plates	
		(b) transfer hatch	5 colonies/plate	
	Pressure differentials		Within specification	
	Glove/sleeve integrity (visual)		No punctures	
Daily	Aseptic room over-pressure		Within specification	
	Cleanliness of aseptic room		Clean	
Weekly	Surface swabs (55mm plate)	(a) work zone	2 colonies/plate	
		(b) transfer hatch	5 colonies/plate	
	Alarm systems		Functioning	
	Glove/sleeve integrity (pressure test)		No leaks	
	Laminar airflow rate (anemometer)		0.3 ± 0.05m/sec	
	Isolator leak test		Within specification	
Monthly	Airborne particulates, unmanned		Work zone	Transfer hatch
	Counts per m^3	>0.5µm	3,500	3,500
		>5µm	0	0
		>10µm	0	0
	Active microbial sampling: operational cfu per m^3		<1	10
Six-monthly	HEPA filter/seal integrity (e.g. DOP test)		Within specification	

This schedule is intended to be for guidance only, and details of frequency of testing and limits should be derived from the literature sources mentioned earlier. Periodic validation tests for equipment, processes and operators (for instance, broth fills) are carried out in addition to the routine monitoring programme.

A programme for routine maintenance of isolators should also be prepared. Given the critical and specialist nature of isolators, routine maintenance and filter changes should be carried out under contract by the manufacturer.

Regulatory issues

Although the MCA has generally accepted the use of isolators in hospital pharmacy practice, there is increasing concern over the emphasis which its inspectors give to microbiological issues, when there is no evidence to suggest isolators are any more vulnerable than laminar flow cabinets.[13]

Similarly, recent moves by the MCA to replace negative pressure isolators with positive pressure devices for cytotoxic drug handling have not been welcomed within the profession. Providing negative pressure isolators are located in an environment of at least EC GMP Grade D, there is no evidence to suggest that product safety is microbiologically compromised.[13]

Production pharmacists are responsible for the safety of their staff and must balance the need for maintaining asepsis with the risk of occupational exposure to cytotoxic drugs. A risk assessment of the processes involved should be conducted in conjunction with the pharmacist responsible for quality assurance, and this should be documented to support the type of isolator (positive or negative pressure) selected.

Future developments

Recent developments in isolator technology include 'safe-change' systems for changing exhaust HEPA filters to avoid occupational exposure to cytotoxic drugs, and hydraulic height-adjustment systems for improved ergonomics.

Gas-sterilised isolators in which the isolator work zone and a single-batch load of components/consumables are sterilised by a gas (peracetic acid, for example) have been used by commercial compounding units for some time. More recently, gas-sterilised isolators have been introduced into hospital compounding units at Birmingham and Swansea, for batch processing.

The operation of this type of isolator has been described previously[14] and gas sterilisation is one approach to dealing with the questionable effectiveness of surface sanitisation of components, particularly in the case of spore-forming bacteria. The main disadvantages seem to be difficulties in validation of the gas sterilisation process and the time taken to process small batches of cytotoxic doses.

Illustration 3: Isolator and load undergoing sterilisation with peracetic acid

An isolator and load undergoing gas sterilisation is shown in **Illustration 3**.

Conclusions

Isolator technology is now accepted in hospital pharmacy practice and is perceived to offer improved safety over class II safety cabinets for the manipulation of cytotoxic drugs. It is essential that the use of isolators is supported by programmes for staff training, validation, quality assurance monitoring and maintenance. Although some regulatory and ergonomic issues remain unresolved, promising developments in isolator design should secure a long-term future for isolators in hospital aseptic compounding units.

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Microbiological considerations in the operation of isolators for aseptic pharmaceutical manufacture

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The microbiological aspects of design, qualification and monitoring discussed in this paper are based on practical experience gained since 1993 of operating isolators for the aseptic manufacture of sterile products. Overall, requirements must mimic those applicable to the conventional cleanroom. However, the inherent threats to sterility assurance which exist with isolator operation will force more demanding programmes, in terms of both scope and time, at each step from design through to routine maintenance and requalification.

The use of isolators for aseptic processing is relatively new. But while there is commonality between the technologies established for conventional cleanrooms and those employed for the same fundamental process using isolator technology, there are also significant differences.

As with all new technologies there are associated risks, and operating difficulties and even failures will occur while experience is being gained.

Within the pharmaceutical industry, the use of isolators in carrying out sterility tests is relatively well established. However, this application is essentially non-critical since process failures will merely result in failed sterility tests, and patient safety will not be compromised. The same cannot be said for a unit intended to aseptically fill a drug product into vials.

To this must be added the fact that many isolators used for aseptic processing are not housed in a Class 100 cleanroom but in an area of lower classification, typically Class 10,000 or 100,000.[1-3] Isolators for aseptic processing are not generally designed to be absolute barriers, nor are they sealed boxes. Thus the normal pressure gradations associated with conventional cleanrooms are absent.

Further, the contact with the process is still often via the gloved hand of the operator, who will actually be positioned within the area at a lower classification than the Class 100 filling zone.

For these reasons, it is clear that design, qualification and monitoring activities must be defined in detail and, given the nature of the aseptic process itself, the microbiological perspective must be fully encompassed. The demands which these activities represent are greater than for conventional cleanrooms, since significant additional design and processing issues must be quantified.

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This paper describes these activities based on experience gained in building and operating such isolators since 1993.[4]

Design considerations

Isolator designs vary considerably in their size, scope and function, and the associated choice of methods to deal with each individual processing step is highly complex.[5] This very complexity can be seen as a strength, in that the availability of several possible solutions better permits an optimal one to be found.

Conversely, developments seen as possible solutions may not in fact be so. Critical issues associated with a specific application may not have been recognised – the risk that is run with all new and developing technologies. As with any project, adequate time must be made available for the all-important design stage, to ensure that good engineering solutions are found and that the microbiological demands have been fully considered.

Room housing for the isolator

For the purposes of this paper, it is assumed that normal design considerations applicable to classified areas will be followed. Thus, for example, drains should be excluded wherever possible. Where this cannot be done, then segregation designs will be paramount, as will the ensuing microbiological sampling and monitoring requirements.

The classification for the room in which the isolator is housed has been a well-debated subject in recent years. The consensus appears to be that a room classified to at least Class 100,000 will be required when an isolator is used for aseptic processing.[1,2]

The specific microbiological considerations relating to the standard of room selected should obviously be such that they can be achieved and maintained routinely. However,