

Handling cytotoxic drugs in isolators in NHS pharmacies

CYTOTOXIC DRUGS

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Introduction

1 This joint Health and Safety Executive (HSE)/Medicines and Healthcare products Regulatory Authority (MHRA) guidance gives advice on factors to consider when selecting either negative or positive pressure isolators for the aseptic reconstitution of cytotoxic drugs. The guidance is aimed at:

- pharmacy managers;
- quality control managers;
- those responsible for training staff;
- health and safety advisers;
- employee safety representatives; and
- those responsible for supplies and purchasing.

The isolator has to perform two functions. It is a key control measure in preventing employee exposure to cytotoxic drugs, many of which are classified as hazardous to health and may also be carcinogens. It also has to protect the aseptic product from microbiological contamination during compounding to prevent infection in compromised patients. This guide will help those responsible for selecting isolators to choose the type of isolator appropriate for both these purposes. It is not intended to give guidance on other aspects of safe systems of work in the pharmacy.

2 Both positive and negative pressure isolators are enclosed systems and rely on large volumes of filtered unidirectional or turbulent air during use to dilute out contaminants. A pressure differential is present on the isolator, which can be either negative or positive depending on use. Isolators are intended to eliminate or control the operator's exposure to the cytotoxic drug during reconstitution, as required by the Control of Substances Hazardous to Health Regulations 2002.¹ In addition, isolators reduce the potential for microbial contamination of aseptic products, as specified in *The rules governing medicinal products in the European Community: Volume 4 Good manufacturing practice (GMP) guidelines*.²

3 Negative pressure isolators are designed to give optimal protection to the operator. Positive pressure isolators are designed to enhance product protection and are commonly used in aseptic production. Air entering and leaving the isolator, whether positive or negative, passes through HEPA filters. A leak on the isolator, such as a hole in an isolator glove or a defective seal, will allow air to directly leave or enter the isolator and bypass the HEPA filters. For a positive pressure system, this will allow air that may be contaminated with cytotoxic drug to enter the workplace. For a negative pressure system, air that may contain bacteria could enter the isolator and contaminate the aseptic product. If the breach is obvious, the isolator should be taken out of use until it is repaired. A regular leak testing programme will ensure that the presence of such defects, whether obvious or not, are identified as early as possible.

4 The period of time between loss of integrity of the system and detection of the leak is crucial. The early detection and repair of leaks should be given particular attention. But, as this is not the only source of operator exposure or of product contamination all potential sources of operator exposure and contamination must be assessed, and appropriate steps taken to minimise risks to worker and patient health.

5 An HSE study in two pharmacy units, one using positive pressure and one using negative pressure isolators,³ found no significant difference in operator exposure to cytotoxic drugs between the units when surface contamination and airborne concentrations were measured. Evidence of absorption by operators was studied by analysis of drugs or their metabolites and the measured absorption was significantly lower than previous published studies, suggesting that a correctly designed, validated and maintained isolator can reduce the risk to the operator, irrespective of the pressure differential.

6 This was only a limited study, but it would seem that in well-managed units, the low levels of exposure and absorption measured were a consequence of factors other than the pressure of the isolators. Only after a significant fault would the pressure of the isolator have a major impact on the operator exposure.

Routes of operator exposure

7 Operators can be exposed to cytotoxic drugs through factors such as:

- breathing air contaminated with cytotoxic drug as a powder, aerosol or vapour;
- skin contact with the drug itself or contaminated surfaces, some of these drugs can pass through intact skin;
- accidental ingestion.

Isolator selection to achieve control of worker exposure and product protection should be a local decision based on factors such as those in Appendix 1 and only a full package of control measures will achieve a high standard of control with either type of isolator. An essential prerequisite for adequate control of both exposure and contamination is a well-trained workforce who is skilled in how to deal with both routine manipulations and the action to take if there is a major leak or spillage inside the isolator. Training should be conducted on a regular basis and be updated when any major change is made to procedures and to ensure that competence levels are maintained.

8 HSE and MHRA cannot stipulate which type of isolator to select. It is possible to use either positive or negative pressure isolators to maximise drug protection and minimise employee exposure. Factors affecting worker health and drug protection should be fully taken into account by means of documented risk assessment, failure modes and human error analysis, together with rigorous change control. Change control requests should be assessed for impact on both product quality and operator safety before a decision is made on implementation. Pharmacy workers and their representatives should be involved in these processes.

9 This document is intended to help in this selection procedure, and to give advice on safe use, for both types. The final choice of which type of isolator to use is dependent on a range of factors. These are discussed in paragraphs 10-19.

Factors involved in employee exposure or product contamination

Factors common to both employee exposure and product contamination

Routine maintenance procedures for the isolator such as glove changes, cleaning of the isolator and filter changes

10 Regular changes of the isolator gloves are essential and this must be performed in a way which minimises possible contamination. Safe systems of work (and safe operating procedures) should be established for changing exhaust HEPA filters. Safe change systems are designed to minimise the possibility of microbial contamination of the new glove. However, there is a possibility that there are cytotoxic drug residues on the used glove and therefore handling and destruction of the old glove becomes an important consideration. Contamination of a floor has been observed when used gloves were dropped after changing.

A significant leak through the containment layers of the isolator

11 This is where the pressure of the isolator may have a considerable impact. Loss of integrity in a negative pressure isolator, ie an inward flow of air, is less likely to give rise to operator exposure, but may cause microbiological contamination of the product. In positive pressure isolators, although some protection is provided, air may enter the isolator by an induction leak mechanism in spite of the positive pressure outward leak, and can compromise the product.

12 A significant leak from a positive pressure isolator may lead to contamination of the operator and the immediate environment. Alarm systems for positive pressure isolators should be sensitive and allow isolator shutdown and rapid evacuation of the room, before any significant exposure occurs. Investigation of the cause of the alarm should be carried out by people wearing personal protective equipment (PPE), which is both suitable and sufficient. Gloves need to resist both permeation and penetration of the drug. Only operators fully trained in the use of this equipment should participate.

13 A significant leak from a negative pressure isolator still requires evacuation of the room, although the isolator should not be switched off.

14 A safe operating procedure for dealing with alarms should be established, including decontamination procedures. This procedure should be practised regularly.

Natural leakage through the isolator

15 This is particularly important for positive pressure systems where any such leakage may result in the escape of cytotoxic drug from the isolator. The significance of the leak will depend on the amount of air escaping and the concentration of the cytotoxic drug in the air. Therefore, working practices should minimise release of cytotoxic drug into the isolator atmosphere and the isolator should be adequately maintained to minimise leakage. The leak detection system should then be able to detect low level losses from the isolator.

16 The higher the rate of airflow through the isolator, at constant pressure differential, the lower the residence time of air inside, and the steady state concentration of drug is reduced. A minimum of 40 air changes per hour is normally required, but different designs may enable adequate ventilation at lower air change rates.

Factors specific to employee exposure

Reconstitution of the drug

17 Transfer of diluent to a vial containing a medicinal product may overpressurise the vial, resulting in the release of air containing cytotoxic material into the inside of the isolator. The actions necessary to remove air bubbles from a syringe may also result in release of contamination in the form of an aerosol or vapour. These activities will be the major source of release of cytotoxic drug into the isolator atmosphere and therefore, every effort should be made to adopt techniques and working practices that minimise releases during reconstitution (and any other transfer activities). Operators should be specifically trained in these techniques and working practices which should be reconfirmed at regular defined intervals. Achieving this will reduce the significance of emissions of cytotoxic drug into the local atmosphere, which may occur if there is a leak from the isolator, although release should be largely prevented by the extraction system in the isolator. If it remains inside the isolator, it may deposit on internal surfaces or on transient materials passing through the isolator and this should be evaluated.

Contaminated surfaces

18 Some cytotoxic drugs can pass through intact skin and this could be a major route of entry into the body. Failure to wear adequate PPE, such as clean and undamaged inner gloves able to resist both permeation and penetration of the drug inside the isolator gloves, may therefore expose individuals to cytotoxic drugs. Control will also be achieved by instigating a cleaning regime at an appropriate frequency in a standard way that prevents contamination build-up. Periodic testing of workplace hygiene practices by undertaking surface wipe sampling should also be considered.

Factors specific to product contamination

19 The isolator provides an effective environment in which aseptic manipulations are carried out and when properly managed prevents microbial contamination of the product when sterile surfaces and materials are exposed. Microorganisms may be present or gain access by the following routes:

- ineffective sanitisation process applied to the resident surfaces in the isolator. If a sporicidal gassing process is used this is less of a risk;
- ineffective sanitisation of the surfaces of transient materials passing through the isolator. If a sporicidal gassing process is used, this is less of a risk;
- transfer into, and contamination of the isolator environment by using non-sterile materials which may include raw materials, equipment, fluids, vacuum connections, gases and lubricants for door seals etc;
- ingress through the physical barriers that comprise the isolator, including:
 - failure of the inlet and outlet HEPA filters;
 - loss of integrity of the operator contact parts of the isolator, such as gloves, sleeves and half or full suits if used. A positive pressure may not provide protection in these circumstances and negative pressure may actively draw contaminants into the isolator.

Combining risk to operator with risk to product

20 As stated previously, there is much more to consider than merely the pressure differential of the system. If the above sources of exposure and product contamination can be minimised, then the type of system selected should be less important. This assumes that there is no catastrophic leakage. In this case, alarm systems and training systems become paramount.

21 The table in Appendix 1 describes the consequences for positive and negative pressure isolators of the critical performance factors for their use. Each type of isolator will bring in some extra specific precautions, and it is up to the pharmacy to assess this based on knowledge of the system. It is recognised that the type used is very much dependent on the exact needs of the individual pharmacy. Therefore, the table describes good practice to help employers select a suitable isolator to prevent exposure.

22 Operator protection advantages of negative pressure and the product protection advantages of positive pressure can be combined into one isolator; this 'double skin' technology is available, although anecdotally not known to be commonly applied.

23 If further advice is required after reading this document, the following sources are recommended:

- the Regional Quality Assurance Pharmacist or any member of the NHS Pharmaceutical Quality Assurance Committee;
- the Medicines and Healthcare products Regulatory Authority general enquiry point at gmpinspectorate@mhra.gsi.gov.uk;
- the HSE website at www.hse.gov.uk.

Appendix 1 Negative and positive pressure: Decision table

The main purpose of this table is to draw attention to the extra considerations arising from a decision to use either a positive or a negative pressure isolator.

Negative pressure	Factor	Positive pressure
<p><i>Product protection.</i> There may be specific requirements for the grade of room where the isolator is located. Usually Grade D is expected provided that leak detection is carried out as described in the 'Leak detection/testing' section in this table. It is important to note however, the negative pressure of the isolator is more critical. These tend to vary from -100 Pa to -300 Pa depending on design. The room pressure should be the minimum required for controlled areas (15 Pa).</p> <p><i>Operator protection.</i> There are no additional air quality standards for pharmacy units above those required for any workplace.</p>	<p><i>Pharmacy environment</i></p>	<p><i>Product protection.</i> Leaks will tend to result in air escaping from the isolator, therefore the room classification becomes less important, however Grade D is expected.</p> <p><i>Operator protection.</i> There are no additional air quality standards for pharmacy units above those required for any workplace.</p>
<p><i>Product protection.</i> Hatches and other transfer devices must be designed to prevent unfiltered air from entering the working zone(s), both in use and at rest.</p> <p><i>Operator protection.</i> Hatches and other transfer devices must be designed to prevent potentially contaminated air from leaving the working zone(s) and entering the room in which the operators are working.</p>	<p><i>Transfer devices</i></p>	<p><i>Product protection.</i> Hatches and other transfer devices must be designed to prevent unfiltered air from entering the working zone(s), both in use and at rest.</p> <p><i>Operator protection.</i> Hatches and other transfer devices must be designed to prevent potentially contaminated air from leaving the working zone(s) and entering the room in which the operators are working.</p>
<p><i>Product protection.</i> The use of aseptic techniques, along with due regard to the direction of airflow, is expected to provide a reduction in the risk that any microorganisms present would contaminate the product. Neither laminar nor turbulent airflow should be assumed to deflect the high velocity jet of potentially contaminated air entering the isolator through a leak.</p> <p><i>Operator protection.</i> Irrespective of whether laminar or turbulent airflow is used, the air should effectively cleanse the space inside the isolator and remove any airborne drug that may be released during operations.</p>	<p><i>Laminar or turbulent airflow</i></p>	<p><i>Product protection.</i> The use of aseptic techniques, correctly devised with regard to the direction of laminar airflow, is expected to provide a reduction in the risk that any microorganisms present would contaminate the product. Turbulent airflow does not provide this element of reduction in risk.</p> <p><i>Operator protection.</i> Whether laminar or turbulent airflow is used, the air should effectively cleanse the space inside the isolator and remove any airborne drug that may be released during operations.</p>

Negative pressure	Factor	Positive pressure
<p><i>Product protection.</i> Minimum necessary to achieve containment objectives.</p> <p><i>Operator protection.</i> The pressure differential should be sufficient to ensure the effective operation of the isolator during all foreseeable operating conditions including cleaning and maintenance, and sufficient to ensure that normal operating conditions do not overwhelm it. Negative pressure should be sufficient to generate a breach velocity of at least 0.7 m/sec.</p>	<p><i>Pressure differentials</i></p>	<p><i>Product protection.</i> Sufficient to prevent pressure reversals and maintain at least 15 Pa at all times.</p> <p><i>Operator protection.</i> The positive pressure differential should be as low as possible, but in line with product protection requirements.</p>
<p><i>Product protection.</i> Rigorous aseptic technique should be used on the assumption that microorganisms may be present.</p> <p><i>Operator protection.</i> Systems of work should minimise the generation of aerosols during drug reconstitution, and prevent drug contamination on the surfaces of vials and interior walls. This is irrespective of isolator type. Methods that minimise product transfer and reduce manipulation should be considered.</p>	<p><i>Systems of work</i></p>	<p><i>Product protection.</i> Rigorous aseptic technique should be used on the assumption that microorganisms may be present.</p> <p><i>Operator protection.</i> Systems of work should minimise the generation of aerosols as with negative pressure systems. However this becomes more important as any leaks may result in contaminated air escaping from the isolator. Methods that minimise product transfer and which reduce manipulation should be considered.</p>
<p><i>Product protection.</i> Training in the special risks regarding leaks.</p> <p><i>Operator protection.</i> Operators should receive adequate training in the hazards and risks of the materials they work with and the steps to minimise those risks. This should include the actions to take if a leak is found, evacuation drills and decontamination procedures.</p>	<p><i>Training programmes</i></p>	<p><i>Product protection.</i> Standard GMP and guidance on isolators.</p> <p><i>Operator protection.</i> Operators should receive adequate training in the hazards and risks of the materials they work with and the steps needed to minimise those risks. This should include the actions to take if a leak is found, evacuation drills and decontamination procedures.</p>
<p><i>Product protection.</i> During installation/qualification carry out distribution leak test including arms and gloves. The pressure decay limit determined in this state sets the limit for routine use. See Note 1.</p>	<p><i>Leak detection/testing</i></p>	<p><i>Product protection.</i> During installation/qualification carry out distribution leak test including arms and gloves. The pressure decay limit determined in this state sets the limit for routine use. See Note 1.</p>
<p><i>Product protection.</i> Identification and monitoring (particulate and micro) of possible in-leak sites. More intensive control and monitoring of the surrounding room.</p>	<p><i>Monitoring systems</i></p>	<p><i>Product protection.</i> Monitoring as appropriate for isolators.</p>
<p><i>Product and operator protection.</i> Gated alarms as necessary.</p>	<p><i>Alarm systems</i></p>	<p><i>Product and operator protection.</i> Gated alarms as necessary.</p>

Negative pressure	Factor	Positive pressure
<p><i>Product and operator protection.</i> COSHH requires that isolators are properly maintained and undergo a thorough examination and test at least once every 14 months. This periodic check should be complemented by regular checks of the system. This may include daily visual checks of the condition of the isolator (in particular any obvious holes or other defects) and pressure gauge readings. These measures would be in addition to routine leak testing.</p>	<p><i>Other maintenance procedures</i></p>	<p><i>Product and operator protection.</i> COSHH requires that isolators are properly maintained and undergo a thorough examination and test at least once every 14 months. This periodic check should be complemented by regular checks of the system. This may include daily visual checks of the condition of the isolator (in particular any obvious holes or other defects) and pressure gauge readings. These measures would be in addition to routine leak testing</p>
<p><i>Product protection.</i> Pinhole breaches in gloves can present the opportunity for air to enter the isolator at sufficient velocity to compromise the product. Visual inspection for leaks before starting operations and systematic examination throughout the day are necessary. It is important that only well-fitting gloves are used to avoid ballooning.</p> <p><i>Operator protection.</i> Holes in gloves still present a risk to the worker, although less than with positive pressure. Permeation and penetration need to be considered in the same way as for positive pressure isolators.</p>	<p><i>Routine use of isolator gloves</i></p>	<p><i>Product protection.</i> Pinholes in the gloves are a potential problem irrespective of positive pressure. It is unlikely that positive pressure will transfer to a glove. Periodic systematic visual inspection is necessary. Accurate glove sizing is less critical.</p> <p><i>Operator protection.</i> Permeation and penetration both need to be considered. Permeation (transport through the glove material) is unaffected by the air pressure. Penetration (leakage of drug through holes or through bad seals) will be increased by positive pressure. In these systems, examination of the glove integrity should be routinely carried out before the isolator is used.</p>
<p><i>Product and operator protection.</i> A system must be in place that ensures that gloves are replaced at appropriate intervals. A safe system of work should be established to ensure that contamination of the worker does not occur during this operation.</p>	<p><i>Isolator glove changing</i></p>	<p><i>Product and operator protection.</i> As for negative systems, a system must be in place to ensure that contamination is prevented.</p>
<p><i>Product protection.</i> Sanitised and impervious inner sleeves and clean inner gloves of an appropriate certification.</p> <p><i>Operator protection.</i> Clean inner gloves should be worn at all times and changed every 30 minutes, or whenever damage or obvious contamination occurs. Clean-room compatible glove liners exist, and there is evidence to support the use of these to prevent skin problems from sweating. Any PPE which may be contaminated by a substance hazardous to health should be removed on leaving the working area, and kept apart from uncontaminated clothing and equipment.</p>	<p><i>Operator clothing/ PPE</i></p>	<p><i>Product protection.</i> Sanitised and impervious inner sleeves and clean inner gloves of an appropriate certification. Standard Grade D clothing.</p> <p><i>Operator protection.</i> Clean gloves should be worn at all times and changed every 30 minutes, or whenever damage or obvious contamination occurs. Clean-room compatible glove liners exist, and there is evidence to support the use of these to prevent skin problems from sweating.</p>

<p><i>Product and operator protection.</i> For in-house quality control purposes, it is possible to measure levels of some cytotoxic drugs in air^{3, 4} or on surfaces. Biological monitoring involving, eg urine samples, is an option for quality control purposes also. However, these procedures need to be optional, involve consultation with employees and be subject to informed consent. See <i>Biological monitoring in the workplace. A guide to its practical application to chemical exposure.</i>⁵</p>	<p><i>Additional procedures. Monitoring and surveillance</i></p>	<p><i>Product and operator protection.</i> For in-house quality control purposes, it is possible to measure levels of some cytotoxic drugs in air^{3,4} or on surfaces. Biological monitoring involving, eg urine samples, is an option for quality control purposes also. However, these procedures need to be optional, involve consultation with employees and be subject to informed consent. See <i>Biological monitoring in the workplace. A guide to its practical application to chemical exposure.</i>⁵</p>
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Note 1. During the installation qualification, a leak test with tracer gas or aerosol and detector will enable the leaks distributed in the isolator to be detected. Once all leaks detected have been eliminated, the isolator can be subjected to the pressure decay test that is to be used routinely. The pressure decay found in this test sets the limit for the routine test. The pressure decay test should include sleeves and gloves. Initially the test should be carried out daily until the stability of the integrity of the isolator is established. Following this, the frequency can be reduced to weekly.

References

- 1 *Control of substances hazardous to health (COSHH). The Control of Substances Hazardous to Health Regulations 2002 (as amended). Approved Code of Practice and guidance L5 (Sixth edition) HSE Books 2013 ISBN 978 0 7176 6582 2 www.hse.gov.uk/pubns/books/l5.htm*
- 2 *The rules governing medicinal products in the European Community: Volume 4 Good manufacturing practice (GMP) guidelines* http://ec.europa.eu/health/documents/eudralex/vol-4/index_en.htm
- 3 Mason H *Cytotoxic drug exposure in two pharmacies using positive or negative pressurised enclosures for the formulation of cytotoxic drugs* Report No HEF/01/01 HSL
- 4 Ziegler E, Mason H, Baxter P 'Occupational exposure to cytotoxic drugs in two oncology wards' *J Occup Environ Med* 2002 **59** 608-612
- 5 *Biological monitoring in the workplace: A guide to its practical application to chemical exposure* HSG167 (Second edition) HSE Books 1997 ISBN 978 0 7176 1279 6 www.hse.gov.uk/pubns/books/hsg167.htm

Further information

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