



Handling cytotoxic drugs in isolators in NHS pharmacies



INTRODUCTION

1 This joint Health and Safety Executive (HSE)/Medicines Controls Agency (MCA) 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 product from microbiological contamination during drug reconstitution. 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 a steady flow of filtered air during use. A slight pressure differential is placed on the isolator, either negative or positive. 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 1999.¹ In addition, isolators reduce the potential for microbial contamination of the product, as specified in the *European Guide to Good Manufacturing Practice*.²

3 Negative pressure isolators are designed to give optimal protection to the operator. Positive pressure isolators are designed to enhance product protection. Air entering and leaving the isolator, whether positive or negative, will do so through the HEPA filters. A leak on the isolator, such as hole in the isolator wall or a defective seal, will allow air to bypass the HEPA filters and to directly leave or enter the system. 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 preparation. If the breach is obvious, the isolator should be taken out of use until it is repaired. A good leak detection regime 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. It is extremely important that the early detection and repair of leaks is given particular attention. But, this is not the only source of operator exposure or of product contamination. It is important to assess all potential sources of operator exposure and contamination and take appropriate steps to minimise risks to worker and patient health.

5 A recent 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. This exposure was measured as surface contamination and airborne concentrations. Evidence of absorption by operators was studied by analysis of drugs or their metabolites. These exposures and the measured absorption were 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 with 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, or 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 has to be a local decision based on factors such as those in Appendix 1. It is the full package of control measures that 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 are 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. This training needs to be conducted on a regular basis and to be updated when any major change is made, to reflect major changes to procedures and to ensure that competence levels are maintained.

8 HSE and MCA 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. Pharmacy workers and their representatives should be involved in these processes.

9 This publication 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 (or safe operating procedures) should be established for changing exhaust HEPA filters.

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, a leak may overwhelm the effect of the positive pressure and 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 need to 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 investigated by people wearing personal protective equipment, 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.

14 A safe operating procedure for dealing with alarms should be established, including decontamination procedures. Procedures should be practiced at regular intervals.

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, you should ensure working practices minimise release of cytotoxic drug into the isolator atmosphere and the isolator is adequately maintained to minimise leakage. Your 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 fluid to a vial containing drug 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. The contaminants can be in the form of an aerosol or vapour. These activities will be the major source of release of cytotoxic drug into the isolator atmosphere. Therefore every effort should be made to adopt techniques and working practices that minimise releases during reconstitution (and any other transfer activities). 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. Such a release should be largely removed by the extraction of the isolator. If it remains inside the isolator, it may deposit on internal surfaces or on transient materials passing through the isolator.

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 personal protective equipment, such as clean and undamaged gloves inside the isolator gloves, may expose individuals to cytotoxic drugs. Control any activities that result in the release of cytotoxic drug into the isolator or pharmacy carefully to minimise these. Instigate a cleaning regime of appropriate frequency and standard that prevents contamination build-up. Consider periodic testing of workplace hygiene practices by undertaking surface wipe sampling.

Factors specific to product contamination

19 The isolator provides an environment in which aseptic manipulations are carried out. If micro-organisms are present in this environment, they may contaminate the product when sterile surfaces and materials are exposed. Micro-organisms may be present or gain access by the following routes.

- Survival of the cleaning and sanitisation process applied to the resident surfaces in the isolator. If a sporicidal gassing process is used this is less of a risk.
- Transfer in on the surfaces of transient materials passing through the isolator. This can occur even though surfaces are sanitized. 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. These may include non-sterile raw materials, non-sterile equipment, non-sterile fluids, non-sterile vacuum connections, non-sterile gases, non-sterile lubricants for door seals etc. Note that if non-sterile materials are components of the product, the product will be non-sterile, but this is not a specific consequence of using an isolator.
- Ingress through the physical barriers that comprise the isolator. These include:
 - Failure of inlet and outlet HEPA filters.
 - Loss of integrity of the operator contact parts of the isolator, such as gloves, sleeves and suits. A positive pressure may not provide protection in these circumstances. Negative pressure may actively draw contaminants into the isolator. In the case of loss of integrity of non-operator contact parts, positive pressure provides some protection, whereas negative pressure will deliver any contaminants in the surrounding room air to 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 sources of 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 You should now examine the table in Appendix 1 and consider what best suits your pharmacy needs. The table describes the consequences for positive and negative pressure isolators on 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 make the decision in the knowledge of what it will entail. It is recognised that the type used is very much dependent on the exact needs of your pharmacy. Therefore the table describes good practice for both types, so that you can ensure safe standards are met when you have made your choice.

22 Operator protection advantages of negative pressure and the product protection advantages of positive pressure can be combined in one isolator; this 'double skin' technology is available.

23 If you need further advice after reading this document, the following sources are recommended:

- Regional QC pharmacist
- Medicines Control Agency general enquiry point: 0207 273 0000 MCA specific isolator enquiry, Andrew Bill: 01904 610556
- Health and Safety Executive Infoline: 08701 545500

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. Where there is no comment, this does not mean that a feature is not important. Other important features may not be detailed below.

Decision table

NEGATIVE PRESSURE	FACTOR	POSITIVE PRESSURE
<p><i>Product protection</i> - There may be specific requirements for the standard of the pharmacy air that may be drawn into the isolator. Usually Grade D is expected provided that leak detection is carried out as described in the 'Leak detection/testing' section on page 5. The room pressure should be the minimum required for Grade D.</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 the isolator, therefore the standard of the pharmacy air become less important. Usually 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. With positive pressure isolators, there is much more potential for this to happen. If positive pressure is used, the standard of transfer devices needs to be higher to ensure that this does not occur.</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 micro-organisms that may be present would contaminate the product. Turbulent airflow does not provide this element of reduction in risk. It should be noted that 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> - Whether laminar or turbulent airflow is used the air should effectively scour 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 micro-organisms that may be 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 scour the space inside the isolator and remove any airborne drug that may be released during operations.</p>
<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>

NEGATIVE PRESSURE	FACTOR	POSITIVE PRESSURE
<p><i>Product protection</i> - Rigorous aseptic technique should be used on the assumption that micro-organisms may be present.</p> <p><i>Operator protection</i> - Systems of work should minimize 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 should be sought. Products requiring little or less 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 micro-organisms may be present.</p> <p><i>Operator protection</i> - Systems of work should minimize 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 should be sought. Products requiring little or less 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 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>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. Limit: individual leaks 20 micron. The pressure decay limit determined in this state sets the limit for routine use. See note 1 on page 6.</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. Limit: individual leaks 20 micron. The pressure decay limit determined in this state sets the limit for routine use. See note 1 on page 6.</p>
<p><i>Product protection</i> - Identification and monitoring (particulate and micro) of possible inleak 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>
<p><i>Product and operator protection</i> - The COSHH Regulations require 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> - The COSHH Regulations require 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 product. Visual inspection for leaks before starting operations and systematic examination throughout the day is 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.</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>

NEGATIVE PRESSURE	FACTOR	POSITIVE PRESSURE
<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.	<i>Isolator glove changing</i>	<i>Product and operator protection</i> - As for negative systems a system must be in place to ensure that contamination is prevented.
<i>Product protection</i> - Sanitised and impervious inner sleeves and clean inner gloves. Possible higher grade clothing. <i>Operator protection</i> - Clean gloves should be worn at all times and changed regularly at least every four hours.	<i>Operator clothing</i>	<i>Product protection</i> - Standard Grade D clothing. <i>Operator protection</i> - Clean gloves should be worn at all times and changed regularly at least every four hours.
<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, for instance, 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. <i>Biological monitoring in the workplace. A guide to its practical application to chemical exposure</i> ⁵ is available by mail order from HSE Books (see below for details).	<i>Additional procedures. Monitoring and surveillance</i>	<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, for instance, 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. <i>Biological monitoring in the workplace. A guide to its practical application to chemical exposure</i> ⁵ is available by mail order from HSE Books (see below for details).

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. The test should be sensitive enough to detect individual leaks of less than 20 microns. 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

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5 *Biological monitoring in the workplace: A guide to its practical application to chemical exposure HSG167 HSE Books 1997 ISBN 0 7176 1279 1*

While every effort has been made to ensure the accuracy of the references listed in this publication, their future availability cannot be guaranteed.

Further information

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For information about health and safety ring HSE's Infoline Tel: 08701 545500 Fax: 02920 859260 e-mail: hseinformationservices@natbrit.com or write to HSE Information Services, Caerphilly Business Park, Caerphilly CF83 3GG.

This leaflet contains notes on good practice which are not compulsory but which you may find helpful in considering what you need to do.

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