



Development and use of pharmaceutical isolation technology over recent years

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When one has to produce or reconstitute a pharmaceutical product, it is possible to consider two distinct approaches to clean environment manipulations. One is the protection of product and the other is the protection of the operator. In many cases, there is a need to do both, and the environment required should be understood by operators and managers to ensure both needs are adequately met. Either a laminar flow cabinet or a pharmaceutical isolator can be used. Each provides a different level of protection, and this paper describes the differences between the two approaches and gives guidance on developments.

Introduction

It is recognised that readers of this journal are from many different and varied backgrounds in terms of their own resources and priorities and may find of interest an article that describes some of the differences between isolators and laminar flow cabinets. It is hoped that this article will be a start for new considerations for some, in terms of both product and operator protection.

There is a significant variation in the use of pharmaceutical isolators in different European countries. It is common practice in some countries for certain preparations in the hospital pharmacy to require protection of the product and/or protection of the pharmacy staff. Such preparations would include the aseptic manipulation of drugs used in cancer chemotherapeutic regimes and preparations of some radioactive diagnostic agents. There is also increasing concern about the adequate protection of some of the newer biological components. There has been an increasing awareness of these practices over recent years and, fortunately, there have been some technical developments in the manufacture of devices to help achieve safer practices.

To illustrate the differences, the most advanced units in certain countries carry out many kinds of preparation including manipulation of virulent organisms and preparations used in gene therapy, in laminar

flow cabinets, and not isolators. In other countries such as France and the UK, most hospital pharmacies prepare cytotoxic drugs in isolators. The former countries may see the use of isolators as an unnecessary encumbrance or an unsound investment, whereas the latter countries are in a development path that ensures protective devices are available through the encouragement of the regulatory authority or the health and safety agencies or both.

There is a well-established group, based in France known as GERPAC (Groupe d'Evaluation et de Recherche sur la Protection en Atmosphère Contrôlée), whose principal aims are to encourage and support research and to evaluate this work which is focussed on controlled working environments for pharmaceutical clean rooms. They are developing guidelines for this type of control and hope to make this available in a number of languages. A similar group, Pharmaceutical Isolator Working Party and User Group, have just published a guidance book 'Pharmaceutical Isolators' and organise Isolator Conferences in the UK.

This article is based on the presentation made at the GERPAC Conference in September 2003 in Lourdes, when my role was to identify and compare the essential properties of laminar flow cabinets (LFCs) and Pharmaceutical Isolators, each of which provide a different level of

protection. It may be logical to start with an overview of some of the differences and similarities of these two types of device.

Isolators and laminar flow cabinets

Similarities: Both laminar flow cabinets and isolators provide a separation of the product from background environment. They also provide product protection, which is the primary aim of each, and they may also provide operation protection. **Differences.** An LFC has an open access from the background environment and so it relies on aerodynamic separation principles to provide the product protection for which it is designed. In contrast, an isolator provides the required separation or containment by either physical or aerodynamic means or, most commonly, by a combination of both.

The physical barrier, which is an integral part of an isolator, provides a more comprehensive containment or separation than is found in an LFC. Isolators require a supplementary device, known as a transfer device, attached to part of the barrier. This provides access to the controlled workspace, or permits an interface between the controlled workspace and the operator.

The level of operator separation differs between the isolator and the laminar flow cabinet. Selection of the most suitable

device in a work situation will need careful assessment of the procedures and operations required.

Members of the specialist ISO committee, Mr Russell Brammah supported by Mr Mike Foster, have devised a schematic that illustrates grades of separation (the 'separation continuum') that may be found in different devices (Figure 1).

Isolator classification.

The original classifications were defined by the UK Pharmaceutical Isolator Working Party for the guidance book published in 1994 [1]. These definitions were for two different types:

Positive pressure (or Type 1) isolator is designed principally to protect the **product** from the process generated & external factors that would compromise its quality and provides a **degree** of operator protection.

Negative pressure (or Type 2) isolator is designed principally to protect the **product** from the process generated and

external factors that would compromise its quality and to protect the **operator** from hazards associated with a product **during operation and in the event of a failure**.

These definitions have now been modified by the ISO to make them more universally acceptable and to reduce misunderstanding in terminology. The definition which appears in draft EN/ISO 14644-7 "Separative Devices" and includes mini-environments and isolators is: *"The provision of assured protection in varying levels by utilising physical or dynamic barriers or both, to create separation between operator and environment"*[2].

There are a number of different types of isolator, which can either be from a standard manufacturer's range or commissioned for a particular application or installation. Variations include:

- Positive Pressure (originally classified as Type 1)

- Negative Pressure (originally classified as Type 2)
- Isolator with rigid walls
- Walls which are flexible film
- Differing numbers of gloves (2, 4 or multiples)
- Access devices which may be half suit or full suit
- Air flows in the controlled workspace which are
 - Unidirectional Flow (Laminar)
 - Non-Unidirectional Flow (Turbulent)
- Special designs to meet particular separation needs

Air flow types

The airflow in an isolator-controlled workspace will be 'non-unidirectional' unless it is controlled in a way to make it 'directional'. This terminology is the preferred one and is more precise than the traditional or popular terminology: 'turbulent' and 'laminar' flow respectively.

Laminar flow is the airflow when the entire body of air within a defined zone moves with uniform velocity along imaginary parallel flow lines. Airflow which is laminar over a surface can be measured indicating that where there is streamlined flow, the velocity profile increases as if it were in layers or lamina from zero velocity at the surface to the main flow velocity some distance away from the surface. It should also be noted that although 'laminar flow' has been in common usage for clean air systems, it does have a different meaning in other areas of science and engineering. The term in the latest standard has therefore been superseded by the term 'unidirectional flow'.

Unidirectional flow air is controlled airflow through the entire cross section of a clean zone with a steady velocity and approximately parallel streamlines. It should be noted that this type of airflow results in a directed transport of particles from the clean zone. Further information is published in BS EN ISO 14644-4: 2001.

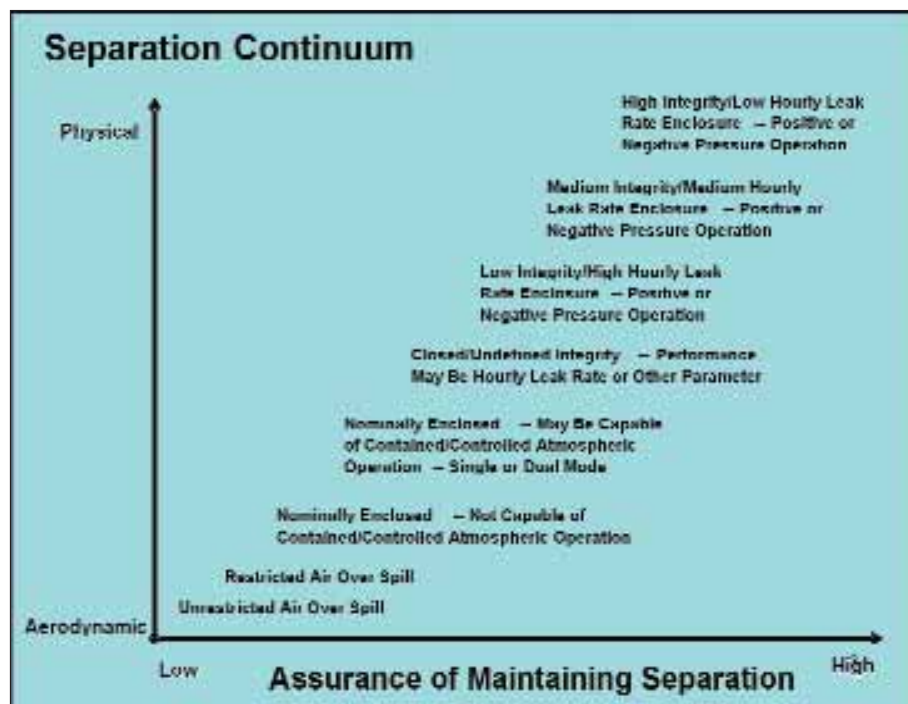


Figure 1. On the vertical axis, this schematic uses increasing values of aerodynamic separation up to physical separation, plotted against the level of assurance of maintaining a level of separation between items in a controlled workspace and the background environment. The plot deliberately does not attempt to enumerate the axes but is used to illustrate concepts rather than quantifiable values.

When we changed from using the term 'laminar flow' and adopted the term 'unidirectional flow', we also abandoned the specific requirements regarding airflow velocity and uniformity of airflow velocity which had been traditionally referenced in BS 5295: 1976. It was this standard that established the air velocity should be 0.45 +/-0.1m/s for horizontal flow and 0.30 +/-0.05m/s for vertical flow. This tolerance applied to uniform airflow and the standard provided a method for calculating velocities on a grid pattern across a cross section of the zone and where measurements should be taken.

Airflow characteristics

After flowing past a cylindrical object in a good laminar flow system, air would reform into laminar flow after the equivalent of three diameters downstream of the object. The reformation of streamlined airflow over irregularly shaped objects is different. As the velocity of the medium increases, whether it is a fluid or a gas, then the consistency of laminar flow decreases. The laminar flow breaks up into turbulent flow and this is known as an edge effect.

It is important to determine the range of velocities within which the air is likely to behave predictably. In an isolator design using a unidirectional airflow, there should be good compliance with the definition of unidirectional flow without too much disruption from typical objects in its path. Initial experimental work showed that air velocities and uniformity of air flow given in BS 5295: 1976 were found to be optimum for unidirectional flow. These values were the same for laminar flow and it is almost certain that the term 'unidirectional air flow' will be used in ISO 14644 Part 3.

On a practical basis, a supplier and the customer should agree the air velocities that

are required for the particular operation and the uniformity characteristics of air velocity to be incorporated into the design. The EC GMP guidance can be used for specifications and it should also be borne in mind that the requirement for 5-micron particles is still unresolved in the revision of Annex 1 of the GMP Orange Guide [3].

It is likely that there will be a new requirement for continuous particle monitoring in the grade A zone. Most operators will not be performing continuous monitoring for an isolator controlled works-

tion from the background environment at a greater level than a vertical LFC. As an isolator is a virtually sealed box, it will have a greater resistance to contamination than either type of LFC. Applying numerical values to these principles will indicate which of these designs will have the greatest risk of contaminating a controlled workspace or compromising the separation of a process from the background environment.

Transfer devices

These are required to enable the use of an isolator in practice. There are a number of different types and these are described and classified in the EN ISO 14644-7 and the new reference book 'Pharmaceutical Isolators' (the "Yellow Guide") [4].

Essentially, transfer devices are used for the transfer of materials into and out of isolators without the transfer of unwanted contamination. Each different application has its own particular requirements and this will need to form part of a User Requirement Specification (URS) and Design Qualification (DQ). Users will need to appreciate that only some transfer devices are air purged and these include types C1, C2 and D. Devices

with separate hatches or doors leading to the background environment or the controlled workspace need to be controlled by timed interlocks. It is also recommended that separate leak testing of transfer devices is a desirable design feature which if present could enable a better monitoring of the isolator.

The isolator - user interface

The isolator will only become useful if there is a meaningful and efficient interface with the user. The Yellow Guide [4] has a list of contents that describe the various items that need consideration. These include: applications; design; transfer and access devices; siting and clothing;

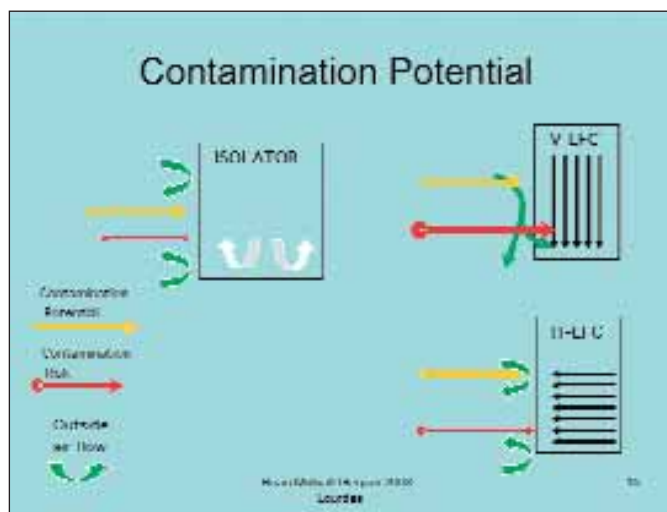


Figure 2. Schematic of the contamination potential for isolators compared to vertical (V-LFC) and horizontal (H-LFC) laminar flow cabinets respectively.

pace and implementing such a new requirement will need careful management. It will be necessary to have a good understanding of airflow characteristics in the environment to be monitored to ensure that the correct and representative measurements are to be made. Such implementation is likely to be prohibitively expensive in some situations.

Contamination potential

The contamination potential for isolators (Figure 2) is different for laminar flow cabinets whether they are vertical or horizontal flow. The air velocity of a horizontal LFC will resist incoming contamina-

cleaning, decontamination and sanitisation; physical and microbiological monitoring; leak testing; validation; standards and definitions. Additional considerations include a training checklist, characteristics of stainless steel suitable for isolators, HEPA filtration mechanisms and carbon filters.

More detailed consideration of the various applications for isolators were classified by a joint working group of Regional Quality Controllers and the Medicines and Healthcare products Regulatory Agency (MHRA) which classified the different types of isolators according to the following criteria: laminar flow, turbulent flow, type of transfer device used, whether they were sporadically gassed or sanitised with alcoholic solutions, whether the products are for immediate use or for batch production. The products were further classified into parenteral, CIVAS (with or without antibiotics), cytotoxic preparations, radiopharmacy agents, gene therapy products, with or without live virus particles and blood products.

Further isolator applications were classified as industrial; when they can be used for sterility testing, powder weighing, micronising, keg sampling and reactor loading or unloading. In filling lines, items for pharmaceuticals, food and drink or medicinal products may be handled.

Laminar flow workstations or isolators?

There is unlikely to be a universally acceptable solution for manipulation. A choice needs to be made either to use a laminar flow cabinet or an isolator. In a comparison between two such devices, the following considerations may be borne in mind:

For laminar flow cabinets: Unidirectional airflow from HEPA filters may be either vertical or horizontal in an LFC. Access to the controlled workspace interrupts the streamlined flow of air. It may be possible to generate standing vortices and unswept areas if items are placed in inappro-

priate positions. LFCs do have an unrestricted access to the work zone and so it is easier to manipulate or process materials in these devices. LFCs are also more prone to contamination from outside the clean zone, so turbulence outside the work zone could contaminate the critical controlled zone. It is not sensible to attempt a leak test on the controlled workspace but it is sensible to test for airflow rate, filter efficiency and particulate contamination as part of the maintenance schedule. The air change rate is controlled by the air velocity over the HEPA filter area of 0.25 - 0.45 m sec⁻¹ standard rate.

For isolators: These may be unidirectional or turbulent flow and access to the controlled workspace will almost certainly interrupt the streamline flow, but this is unimportant if the air is already turbulent. Standing vortices and unswept areas are possible but are less likely in turbulent flow isolators. Again, this will depend on the configuration or position of devices placed in the controlled workspace. Access to the work zone is restricted by the envelope of the isolator, which may make it more difficult to manipulate the devices. This restriction will also make it more difficult to contaminate the work zone, but it should be remembered that contamination of the controlled workspace will occur through transfer devices if conditions are not well controlled. Leak testing of the enclosed space is practical as it can be defined and is usually delineated by the isolator envelope. The high air exchange rate for the volume of the controlled workspace of up to 200 air changes per hour and higher is easily achieved.

Conclusions

From this fairly rapid summary of some of the features of isolators and laminar flow cabinets there are a number of conclusions that may be drawn.

Operators should understand the type of equipment that is being used. It may differ for different applications and so training may be needed to ensure this understanding is

complete or at least at an optimal level. Whether an isolator or laminar flow cabinet is best depends on the application, which in turn depends on a number of factors. Each factor should be carefully considered to try and ensure that risks to the product remain well controlled.

Future developments in technology need to be taken into account. Innovative technology may provide better solutions to a problem or system. The complete system should provide optimal operator and product protection.

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References

1. Lee, M.G., Midcalf, B (eds.). Isolators for Pharmaceutical Applications. London: HMSO (now (the Stationery Office), 1994. ISBN 0-11-701829-5. Price: £19.95.
2. BS EN ISO 14644 Part 7: Separative devices (clean air hoods, gloveboxes, isolators, mini-environments) Draft, FDIS (in preparation)
3. Rules and guidance for pharmaceutical manufacturers and distributors 2002. London: The Stationery Office, 2002. ISBN-0-11-322559-8. Price: £24.50. (Also known as the "Orange Guide").
4. Midcalf, B., Phillips, W. M., Neiger, J. S., Coles, T. J. (eds.). Pharmaceutical Isolators. London: Pharmaceutical Press, 2004. ISBN 0-85369-573-3. Price: £29.95

Further Information

University of Leeds TSET & PTQA courses (www.tset.org.uk or www.leeds.ac.uk)

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