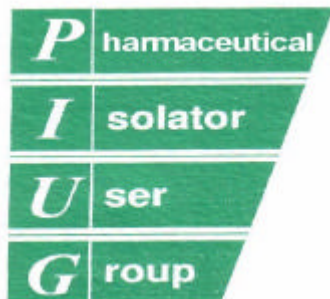


Pharmaceutical Isolator User Group Newsletter



Special points of interest: in this issue

- Editorial
- Conference number 5 Report
- Ways of looking at leaks
- News Items in brief
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Editorial

Welcome to Edition 5 of the newsletter.

The purpose of this newsletter is to provide specialised information to users of Pharmaceutical Isolators. There are still many aspects of Isolators that are causing some concern with the users and managers of the services that use Isolators.

We are still not achieving some of the objectives of this newsletter and I hope you, as a reader, are able to help us develop. I am confident that you are probably willing to help us improve communications between users but probably haven't quite got round to writing anything done yet! It is difficult to know the best way of helping you communicate with us but we are developing a website, have email, fax and telephone communications so all this should help.

We would like you to make a small contribution in the way of a comment or question. We very much appreciate a larger article describing some special Isolator interest of yours or a technical dissertation.

Topical news includes a recent communication from the HSE indicating that their report on some of the risks relating to handling hazardous sub-

stances in positive or negative pressure Isolators is nearing completion. The deliberations of the ISO group in developing standards is progressing but will not be available until 2001 or later. The Working Party has been meeting during 2000 and 2001. It was accepted that to wait until the ISO group had completed their deliberations was unacceptably long in relation to publication of Edition 3 of the 'Yellow Guide'. We have therefore committed ourselves to go ahead and revise and extend this useful book as soon as possible and this should become available mid 2001. The 5th Isolator Conference was well attended and generally regarded as a success by the majority of delegates, speakers and exhibitors.

The next (6th) Isolator Conference is to be held on October 28th–30th. If you know of a particularly suitable venue for future Conferences, please let us know. Venue reservations need to be made well in advance. If you would like to present a paper, short communication, poster, lead a seminar please let us know and we will try and fit you into a future Conference schedule. Any other comments or advice would also be appreciated.

Free Advertising is available for the next issue. It is normally charged at a mere £50 when you can purchase a half page advertisement in the Newsletter. It is hoped that you regard this as an extremely attractive offer, (especially for the next issue) and an opportunity to inform a targeted audience, interested in Isolators, about your specialist services and your specialist equipment, whatever this may be!

All the contact details are on the last page of the newsletter so we look forward to hearing from you.

Colour or Black and White

This issue of the Newsletter is in glorious colour. As reproduction in colour is expensive we have had to settle for a quick edition in glorious monochrome. To produce 500 copies in colour would cost £300 – £400. Perhaps your organisation would like to sponsor an edition. If you would like to help please contact your User Group Chairman.

Would you benefit from seeing your Company name displayed here. You could have your name noticed by a target audience for a very reasonable cost as well as the satisfaction of knowing you were helping support the publication of this newsletter. Contact IUG committee

So Your Isolator Leaks!

Following the comment about leaking Isolators in the last issue, I will remind you of the comments made then and go on to provide more information on how to assess the significance of such leaks. I will again ask you for your views on this so we may try to obtain a better perspective on this problem.

The MCA Inspectorate is developing an ever greater level of understanding of Isolator technology. If you have a licensed unit you may have already been asked to quantify the leak rate of your Isolator. If not, then when your next inspection is due the question may be asked then. For unlicensed units, there is an increasing level of commissioning, validation, and testing going on so there will be more data available that could be used for calculation of leak rates.

An inspection in Leeds licensed Pharmaceutical Manufacturing Unit referred to the question about the rate of leak from our production Isolator. Having been relatively content with a knowledge of the time it takes for a pressure drop to occur between defined limits, it apparently seemed reasonable for us to have a better knowledge of the actual size of the leak. The question we could not answer at the time of the Inspection was 'What is the leak rate expressed as an equivalent hole size?'. In other words, a pressure drop knowledge is all very well but what does it really mean? Is 5, 10, 20, 50 pascals reasonable for your Isolator or does it mean we have a serious leak. If all the leaks were to be combined into a single hole, just how big would be that hole.

I am indebted to John Neiger and Time Coles for the fundamental consideration of leaks and how to measure such leaks. If you have scanned ahead in your reading and do not much care for mathematical explanations all I can hope you will note is 'don't panic' the maths is quite simple and the principles of physics described and the ones you have probably already met and knew but may have forgotten. This will be a reminder to give a better understanding of what is going on and is something you ought to understand anyway. For the engineers and scientists you will be able to scan through the following as a reminder and it will be something you probably know but may not have considered.

There now follows a number of leak test formulae to place things in perspective. The first deals with the Gas Laws. Essentially these laws describe the relationship between temperature, pressure and volume of a gas. If you have a sample of gas in a container, a jar, a cylinder or even an Isolator then if the temperature changes so will the pressure, assuming the volume remains constant. If the pressure changes and the volume remains the same, then the temperature will alter. If the volume is allowed to change then the pressure will change if the temperature remains constant or the pressure will stay the same if the temperature alters.

These potential changes need to be considered when an Isolator is checked on a daily basis, for example for a pressure decay test. If the room temperature or the Isolator controlled work-space changes whilst the test is carried out, or the atmospheric pressure alters, then the test results will be affected. These relationships are expressed in the Gas Laws which makes equivalent the ratios of initial pressure (P_1), volume (V_1) and temperature (T_1) to the final pressure (P_2), volume (V_2) and temperature (T_2).

The Gas Law states:
$$\frac{P_1 V_1}{T_1} = \frac{P_2 V_2}{T_2}$$

If a calculation is required then the units must be considered as they are for P in Pa, T is in degrees absolute and V is in m^3

For the same temperature during the measurements, where T is constant, then the equation is simplified to ignore temperature.

$$P_1 V_1 = P_2 V_2$$

This can be rearranged to determine the second pressure P_2 in terms of the first pressure and the initial and final volumes.

$$P_2 = \frac{P_1 V_1}{V_2}$$

Using the different volumes implied after a pressure decay test then if there is $n\%$ leakage difference the new volume after the test can be calculated.

If there is leakage of $n\%$, then

$$V_2 = V_1 \left(1 + \frac{n}{100} \right)$$

And substituting for V_2 in the above equation Thus,

$$P_2 = \frac{P_1 V_1}{V_1 \left(1 + \frac{n}{100} \right)} = \frac{P_1}{\left(1 + \frac{n}{100} \right)}$$

And using the pressure increments to assess for differences in pressure

$$\Delta P = P_1 - P_2 = P_1 \left(1 - \frac{1}{1 + \frac{n}{100}} \right) = P_1 \left(\frac{n}{100 + n} \right)$$

or
$$n = \frac{100 P_1}{P_2} - 100$$

So we now have an expression which gives the percentage volume of leakage in a given Isolator. If we use this formula with some values we can see how it will work.

Suggesting a test pressure of 250Pa, with 0.5% volume loss per hour allowable:

$$\Delta P = 100,250 \left(\frac{0.5}{100.5} \right) = 499 \text{ Pa}$$

Using a 10 minute test.

Hence,

$$\frac{499}{6} = 83 \text{ Pa drop}$$

So now we have determined a pressure drop for a type of Isolator we now need to calculate the SHE or single hole equivalent.

The area of this single hole is given by the volume of air passing through this imaginary orifice divided by the velocity of this air:-

$$\text{area of hole (m}^2\text{)} = \frac{\text{volume flow (m}^3 \text{ sec}^{-1}\text{)}}{\text{velocity (m sec}^{-1}\text{)}}$$

Further consideration of the velocity relates to the pressure difference and the density of air passing through it.

$$\text{velocity} = \sqrt{\frac{2P_m}{\rho}} \equiv \sqrt{\frac{2P_m}{1.225}} \quad \text{where } P_m = \frac{P_1 - P_2}{2}$$

So

$$\text{volume flow} = \frac{V_1 \times n}{100 \times t} \text{ m}^3 \text{ sec}^{-1}$$

where t = duration of test in seconds

or

$$a = \left\{ \frac{\frac{V_1 \times n}{100t}}{\sqrt{\frac{2P_m}{1.225}}} \right\} \times 10^6 \text{ mm}^2$$

Using some of the above derivations we can try these on an Isolator which is reasonably large at 5 m³ volume. The pressure decay readings could be typically as follows:-

Isolator =	5 m ³	
Start Pressure =	140 Pa	
End Pressure =	110 Pa	
Time =	10 minutes	

Single Hole Equivalent:

If you need to calculate what is the equivalent hole size of the leak from the pressure decay tests this is one of the

ways it can be done.

$$a = \left\{ \frac{5 \times 0.03}{100 \times 600} \right\} \times 10^6 \text{ mm}^2$$

$$\frac{2,000 \sqrt{\frac{a}{p}} \text{ microns}}{p}$$

$$a = 2,000 \sqrt{\frac{0.175}{p}} = \underline{472 \text{ microns}}$$

Having done such a calculation, it is interesting to note that, in the example chosen, the size of the hole is not very great. If we now speculate how significant this is, it may help to judge how big a risk is presented to the operator or to the product.

Having indicated the hole is small, bacteria are very much smaller. How big is the risk of contamination? What does it depend on and how contaminated is the background environment? We also need to remember we have just calculated a single hole equivalent. It is reasonably likely that your Isolator will not just have the one hole. So are we any nearer to estimating the risk of contamination? How large will the largest hole be? What will become an acceptable pressure drop for your Isolator?

I look forward to views and comments for future newsletter issues.

Help Wanted.

It would be interesting to collect this type of data from a number of different Isolators. Would you help by doing some similar calculations and passing on the information? We will generate a table of results for members to see so we can judge just how 'leaky' are our Isolators. If you send in your calculations we will need the dimensions of the Isolator and the type (+/-ve) together with the class of transfer device.

There have been a number of engineering considerations relating to leaks, how they may occur, what effect they may have, how big a risk they may be to either product or operator, the concept of jet velocities and more.

For unlicensed units; you are subject to audit by your friendly Quality Controller. Where the MCA lead the QC auditor is likely to follow. This level of understanding may be a more widespread requirement than you may have thought. The above information may be helpful.

People Profile

This is an opportunity to get to know a little about your User Group Committee. We have experienced a natural reduction in numbers down to about 6 regular workers on the committee. These are:

Ken Baker. Ken joined the committee, bringing with him the valuable specialist experience relating to gloves and gauntlets. Although Ken is essentially retired, he has many contacts from his specialist Associates links. Such links were mostly in the nuclear industry and it is vitally important that access devices like gloves and gauntlets were well controlled. Although Ken has some limitations on travelling due to health reasons, he is always enthusiastic about matters relating to Isolators and his connections have been valuable in the planning of Isolator Conferences. Ken will also be involved in the forthcoming conference.

Caroline Coles. Caroline is a founder member of the committee. She has brought a very significant drive and enthusiasm to the group. She played an important role in the production of the first newsletter and her background of the Institution of Containment and Isolation was a useful communication base in the establishment of speakers for conferences and courses. Her background of organisation and management and been one of assets in the group. Caroline now runs a new Isolator supply company which will exclude her from many more activities in the committee

Beverley Ellis. Bev is a specialist Radiopharmacist at the Nuclear Medicine Department, Manchester Royal Infirmary. She has been a member of the UK Radiopharmacist specialist committee for some years and has a good clinical relationship with the Nuclear Medicine Department in this specialist hospital. Bev is a relatively new member of the committee but has brought a wealth of enthusiasm to the group. One of her specialities is training and she is combining her experiences with Lynn at the forthcoming Isolator Conference. Another specialist interest is in Internet Web design. Her position on the National education and Training Group TSET is one of 'Web Mistress'. This experience was tapped to start the generation of the PIUG website.

Margaret Horsey Margaret has been one of the founder members of the committee. She has been acting as treasurer although the funds are held within the University and she has not been required to perform normal treasurer duties. She has been a pharmacist who has specialised in quality control and performed this

important role from her base hospital in Rotherham. Recently Margaret has taken up a QC pharmacist post in Bradford. Here she has a quality role in a large aseptic services unit and an audit responsibility for the local hospitals.

Lynn Lawler. Lynn is employed by Baxter Healthcare as a Quality Supervisor, based in the Aseptic Dispensing Unit at Manchester Christie Hospital. Here she leads a team of dedicated technical staff who prepare a range of aseptic products for use in the hospital. Baxter utilises gassed sterilised isolators, Lynn is responsible for monitoring and maintaining this equipment which includes training of operators in their use and management of the validation program to ensure compliance and maintenance of the quality system. Baxter also collaborate with other local hospitals to provide their needs for specialist treatments. The company regard Lynn as a specialist in one of the most important elements of any system; Quality and Training. She has recently been involved in updating company systems and ensuring the staff have the best possible support. Lynn's specialist role in the User Group is that of Secretary. She also participates in Conferences and will be leading a training seminar in this month's Isolator Conference.

David Morley. David has also been a founder member of the committee. From a specialist microbiology education, he has developed expertise in validation of mostly industrial systems and procedures. David is now employed as a consultant and is involved with a number of companies in a range of validation projects. He has been a member of the well established Scottish Society S²C². David is also a recognised presenter, particularly of validation issues, at recent conferences and training courses. He will also be involved in the forthcoming conference. There is much travelling in his life style but if time permits, it is time itself that has an appeal, as David is an official timekeeper for vintage car rallies for which there is a long established enthusiasm.

Questions and Answers

Q We have a 10 year old Isolator running at negative pressure. It is used to dispense cytotoxic drugs aseptically. The Isolator is in a dedicated room and exhausts into the room. The staff operating the unit are concerned about their exposure. Should the old Isolator be replaced ?

A The level of aseptic dispensing is at a low level, only a few units a day and not every day of the week. Measurements of any room environment contamination had not been done so it was recommended that suitable analytical measurements could be made. If there was any cytotoxic drugs found then the situation was more serious and leaks should be investigated.

The Isolator is tested regularly and it always passed the normal monitoring tests

Q We use a negative pressure Isolator for Cytotoxic preparations. Do we have to vent the exhaust to the outside? We are not on an outside wall so can we use a carbon filter instead? What precautions do we need to take?

A -anyone please help -

PIUG on the Web—Status Report

There was a comment in the last newsletter indicating that we were hoping to have an active website by the time the next issue was published. A design was completed in early Autumn 2000 and much of the initial material was posted into the linked pages. Some agreement was reached for links to relevant organisations and after further delays, the necessary web addresses were incorporated.

The website has been developed and became live in July 2001. It provides information and links to other relevant sites. A form to ask for information, register for membership and for conferences has also been generated. Information entered onto these forms is sent directly by email to the administration office at Leeds University (Samantha Armitage)

The newsletter is ready to be posted onto the website and future information will be generated in a similar manner.

If your organisation or company would like to be linked to our website please let us know. We would be anxious for the web IRL to be linked to you in exchange and in this way communication should improve.

Conference Report

The 6th Pharmaceutical Isolator Conference is to be held at The Cairn Hotel, Harrogate in North Yorkshire from Sunday evening 28th October to Tuesday 30th October 2001. The venue is a recently refurbished hotel just to the north of the town centre with good facilities. The main conference venue will be the hotel ballroom and we are arranging good quality audio visual equipment. There are suitable facilities to be used for the seminar sessions and good break out areas. Access to the exhibition area is easy from both the exhibitors and the delegates point of view. The Conference will again be administered by the School of Continuing Education, University of Leeds.

Many current topics relating to Isolators are planned. There will shortly be a new International Standard relating to what we understand to be Isolators. Preceding this, there is to be a revision of the 'Yellow Book'. The new publication was planned to be available in time for the Conference but with so many new sections to check this target is unlikely to be met. There should be a demonstration copy available for consideration by delegates on the PIUG stand.

The Conference program will include presentations on the positive and negative Isolator debate and where or how these should be used. We will have an opportunity to compare the developing new ISO standards with other recognised standards. There will be sessions on maintenance and validation, use of biological indicators, training, practical and user experiences. There will also be a poster session and an appraisal of innovations from manufacturers. One of the most important aspects is the general discussion and interaction between delegates as lots of questions can be asked and much information exchanged. This will be in addition to the scheduled discussion session during Conference.

6th Pharmaceutical Isolator Conference

For further information please contact:

Mr Brian Midcalf

Chairman Isolator User Group

Please register your interest by contacting Samantha Armitage Department of Continuing Education, University of Leeds.

0113 233 3236

Email: s.armitage@leeds.ac.uk

New 'Yellow' Guide—Progress Report

The Isolator Working Party has been working very enthusiastically to produce the new edition of the popular User Guide, 'Isolators for Pharmaceutical Applications'; affectionately known as the 'Yellow Guide'

The group have been fully aware that the Guide was in need of revision for some years now. It was decided that we needed to wait for the development of the new ISO Standard to avoid any potential conflicts with the revised Guide.

The Group started the work in 2000 after considering the potential conflicting demands of users and the setters of standards. Initially, knowing there was going to be a standard developed by ISO it was accepted that we would delay the development of the next user guide until the standard terminology had been agreed. This was sensible as a user guide using a set of different terms to the Standard would likely cause confusion and misunderstanding.

As time past, we realised that the most optimistic schedule for the ISO development was subject to a serious of set backs or delays. There was also an ever increasing demand for the new edition of the 'Yellow Book'. The Working Party set about developing the new guide. It was to be expanded significantly and have more explicit, user friendly guidance for all Isolator practices. The problem of terminology conflicts was to be resolved as far as possible by using the development information made available from the deliberations of WG7. It was then likely that there would be very few conflicts.

We agreed therefore that we should make progress on the 3rd Edition as soon as we could. The mechanism of gathering the information for the text was an interesting challenge to the group.

After some discussion, we readily agreed to form groups from our membership. A member was selected as section leader following the particular speciality or interest of the individual where possible. The group members then combined their expertise and when a chapter has enough agreement it was circulated for wider comment to the whole WP.

To facilitate all this combination of effort, the modern communication methods were adopted. This meant the Internet with its email communication systems helped enormously in the exchange of material.

The agree main sections of the book are as follows:

1	Introduction
2	Definition of Terms
3	Design
4	Transfer Devices
5	Siting and the Environment
6	Validation
7	Training
8	Gloves and gauntlets
9	Applications for Isolators
10	Standards
11	Cleaning, sanitisation and decontamination
12	Leak testing

The aim was always to produce a book which would be used by many Isolators users in a wide range of different situations. It was to be a practical and useful guide. This objective is still a main focus of the Group.

Another objective was to produce the book in time for the next Isolator Conference. We have given an assurance that this would be maintained. During the last year very good progress had been made. Although our target was in sight, with so much material from different groups, the editorial process was becoming a very time consuming business. A small group has been making very good progress in the editorial screening but there is still more work to do.

As more of the main Working Party saw, considered and criticised the assembled chapters of the book, suggested additions were made. The realisation that some items had not been included immediately stretched the completion date. These factors are responsible for an extended final completion date.

Recently the Working Party agreed that it would be unwise to release a book that was not complete or a book where errors had not been corrected. Neither did we think it was wise to release part of a book. We do hope to exhibit a computer version of the latest draft so that Conference delegates can see how much progress has been made. It will present an early opportunity to receive feedback from potential users.

The outcome of all this is the realistic prospect of the publication of the new edition in 2002. We hope to have both a printed and CD Rom version available and the normal printed copy will be published via the Pharmaceutical Press.

Meanwhile the current edition 2 is still in print.

A Sick Isolator Story (continued)

Message for sick Isolators



I am a sick Isolator. I said that last time. I am still not feeling too well. In fact, I am only improved because I am receiving some attention.

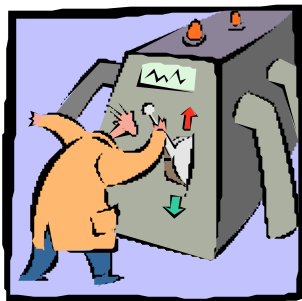
Just receiving attention doesn't mean I am going to be cured but at least there is a ray of hope.

ENOUGH IS ENOUGH!

I said before that I was looking for other Isolators in a similar state to contact me to share experiences. Where are you? Is every other Isolator but me in peak condition? Is the situation so much better than I had first been led to believe? Or is it even more serious than I had at first thought? You may be so sick that you haven't the strength to put pen to paper. Maybe your electronic plug has been pulled!



Just as a reminder; some of you might now be or



may never have been quite up to the required standard Seals loose, rusty bits, handles falling off, HEPA filters with holes in them rickety hinges, faulty gauges..... Some of you may not have been tested properly and your ailment may not have been picked up.

Are you struggling on, day after day, not really being able to reassure your owners that you will provide the required environment in which they must prepare their products or carry out their procedures.

I've just heard! At the next Conference to be held this month someone is going to discuss some Isolator disasters. I understand there are some amusing tales to relate. I will keep my ailing sensors tuned as best I can and report back in the next issue.

Why not put your Isolator in touch with the unit featured above? There may be comfort in the comradeship of other units facing a similar problem. If these neglected Isolators can register with the User Group as associate members who knows how such a united approach could dramatically improve the controlled environment required by so many of us. Please send your neglected Isolator's list of problems to the editorial team.

Advertising Feature



Pharmaceutical Isolator User Group

How to contact us:-

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 Email brian@midcalf.club24.co.uk

Mrs Lynn Lawler
 Ms Margaret Horsey
 Mr David Morley
 Dr Bev Ellis
 Mrs Caroline Coles
 Mr Ken Baker

Your Contributions Wanted....

Experiences required!
 Beginners problems?
 User Difficulties?
 Hints and Tips to offer?

Please write or fax or email your comments and contributions to:-

Mr Brian Midcalf at the above address or to any member of the User Group Committee

or to

Ms Samantha Armitage
 School of Continuing Education
 Springfield Mount
 University of Leeds

The Isolator User Group was created following a number of successful Pharmaceutical Isolator Conferences. These events drew together delegates involved in the use of Isolators, the design, construction and testing of Isolators as well as specialists in associated fields. Delegates to these conferences formed the nucleus of the User Group. A committee was elected and officers appointed to run the User Group.

The objectives of the Group are to promote good practice in the use of Pharmaceutical Isolators; to provide a forum for the exchange of information; to promote a platform for discussion on any isolator topic, to deliberate over testing and evaluations associated with Isolators and to facilitate training.

There is considerable support for a wide range of membership, within the UK and in other neighbouring countries. If you are reading this and you are not a member we would be pleased to hear from you and indicate how you could join our group for a modest subscription. Contact any of the User Group Committee or Email the chairman.

Chairman: Mr Brian Midcalf

Secretary: Ms Lynn Lawler

Treasurer: Mrs M Horsey

Committee::

Mr Ken Baker, Mrs Caroline Coles, Dr Beverley Ellis, Mr David Morley.



A suitable venue for a conference?