THE USE OF NEGATIVE ISOLATORS FOR CYTOTOXIC RECONSTITUTION

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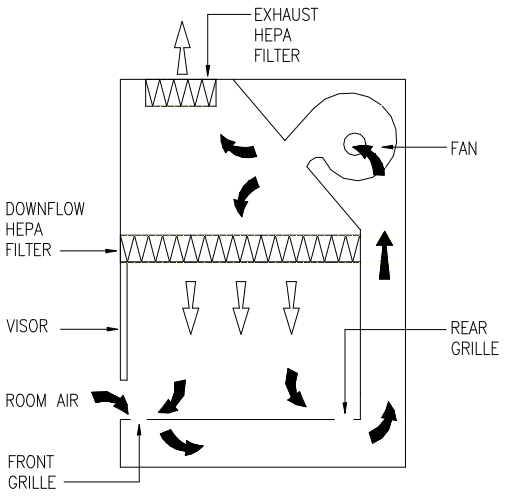
The United Kingdom is unique in that probably 90% of all cytotoxic reconstitutions in hospital pharmacies are now carried out in isolators. Most of these isolators are negative pressure. Other countries are starting to follow this practice, notably Australia at one end of the world, and Scandinavia at the other.

In Germany and the United States particularly, Class 2 Biological Safety Cabinets are still recommended and widely used for this application. The 1995 publication of the ASHP "Principles of Sterile Product Preparation" shows a diagram of a Type A Class 2 BSC. The author has visited hospital pharmacies in the USA where such cabinets are in use for cytotoxics.



"Class II Type A Biohazard Cabinet as widely used in the USA for the dispensing of cytotoxics. The author challenges this application."

It is necessary to question how such a Class 2 BSC provides protection to the technician. It does this by means of an air barrier at the front aperture. The effectiveness of the air barrier may be measured by generating an aerosol inside the working area of the cabinet and measuring what proportion of the aerosol escapes. It is generally accepted, for example in the new European Standard for

Microbiological Safety Cabinets, EN 12469, that at the type testing stage, the effectiveness of the air barrier should be a minimum of 10^5. This means that with the air barrier in operation, the number of aerosol particles reaching a defined sampling point is less, by a factor of 10^5, than would be the case if the air barrier was not there. In theory therefore the air barrier appears to be effective. However, the measurement of the effectiveness is usually made in ideal conditions, conditions that do not exist in a typical busy hospital pharmacy. For example, personnel may be walking by. A door may be suddenly opened. Diffusers for the room air ventilation may be creating draughts. Worst of all, the technician is moving his hands and arms as he works and, from time to time, withdrawing his hands completely. With this latter action, he does not just disrupt the air barrier, he may also transfer contamination out of (or into) the cabinet on the surface of his gloved hands.

In many parts of the world, the effectiveness of the barrier is only measured at the type testing stage. It is not measured after installation, nor routinely in use. This means that even with the air velocities of the cabinet properly set up; there may be extraneous influences that effect its performance. Only in the United Kingdom and Australia are the air barriers of Class 2 Cabinets tested on installation and routinely thereafter as a matter of course. Test houses in the UK have records of Class 2 cabinets that have passed the test one year and failed the next because something has changed in the laboratory. This suggests that regular flow visualisation tests and/or anemometer readings of air velocities are not sufficient to confirm that the air barrier is working effectively.

Another reason to question the safety of Biological Safety Cabinets for use with cytotoxics is precisely because they have been designed for dealing with biological hazards. Such hazards can be inactivated by fumigation, usually with formaldehyde. Cabinets that are used for cytotoxics (or indeed any chemical hazard) need to be designed differently, so that all areas inside the cabinet that might become contaminated are fully accessible for cleaning. This is not the case in the Class 2 Cabinet shown in the diagram. Contaminated air can go down underneath the worktray, up the back, through the fan and finally to the exhaust filter and the downflow filter. The whole of the inside can become contaminated.

Therefore the widely used Class 2 Biological Safety Cabinet may not be as effective in protecting technicians, and indeed the surrounding area, from cytotoxic contamination as has been previously thought. Indeed there are now many published papers, mainly from Holland and the USA, which report traces of cytotoxic contamination in the pharmacy and on pharmacy staff where such cabinets are used. If this is disturbing to all those who are using conventional Class 2 Biological Safety Cabinets for handling cytotoxics, the author acknowledges that that is his intention!

At a recent international conference of oncology pharmacists, there was an interesting poster from Australia. It concerned the use of "Cytotoxic Drug Safety Cabinets". To quote from the poster: -

> "The main differences (as against Biological Safety Cabinets) are the inclusion of HEPA filters both above and directly below the work zone, thus keeping the internal plenums, fans and the supply filter free of solid contaminants and an activated carbon filter downstream of the exhaust HEPA filter to provide protection for volatile drugs."

So the Australians have recognised and addressed some of the problems of using Biological Safety Cabinets for cytotoxics, and they have also incorporated an activated carbon filter in anticipation of the recent revelations regarding cytotoxics that sublimate, i.e. pass straight from the solid phase to the vapour phase.

However, the poster did not say is that the Australians now have a standard for cytotoxic isolators – the first national standard on this subject – which takes all of this one big step further.

The first and obvious advantage of an isolator is that it provides a total physical barrier. The human being, the greatest source of contamination in any working environment, is removed from the working environment. At the same time, he is better protected from contamination, e.g. cytotoxic contamination that might be generated inside it. The second advantage is that the technicians access to his work is faster. Isolators do not have to be sited in full cleanrooms so the changing or gowning process to enter the isolator room is much simpler and quicker. The third advantage is that the working position is much more comfortable. In a Biological Safety Cabinet, the operator must work with his arms straight out (so the critical work is in the 'first air' of the laminar flow) and without resting arms on the work surface (which would be very bad practice). In an isolator, the technician can rest his arms on the shoulder rings of the isolator and work in a comfortable position. This is further facilitated still further in recent designs of isolator which incorporate raising and lowering devices within their stands. The fourth advantage is that the isolator is not at all sensitive to air movements in the room. The fifth advantage is that the background environment is less critical than it would be for an equivalent laminar flow cabinet. The sixth advantage is that the running costs for an isolator are lower, mainly because the cleanroom clothing regime required is much less stringent.

Laminar flow negative isolators were first developed in the late 1980's. The requirement was for a glovebox (like the Class 3 Biological Safety Cabinet) with the laminar flow characteristics of the Class 2 Biological Safety Cabinet. The first designs were in fact based on Class 2 designs. Very simply, a visor with gloves replaced the open front and air was introduced through the filtered tranfer

chambers at each side instead of through the open front. This gave the added benefit of a high air change rate in the transfer chambers, which were thus able to purge quickly and dry off surfaces wet with disinfectant quickly. Present designs are very much on the same principles.

In recent years, the regulatory authorities (MCA) have become concerned that if a negative isolator leaks, the leak would be inward and contaminated air from the background environment could enter the isolator and contaminate the product. Theoretical calculations by the author have demonstrated that provided the isolator is sited in a European GMP Grade D area, the risk of such contamination is probably very low[1].

Another issue that has been widely reported recently is the possibility of certain cytotoxic products such as cyclophosphamide existing in vapour form[2]. Clearly, HEPA filters do not stop vapours. Alternatively, where aerosols are stopped by HEPA filters, they may later sublimate! The effectiveness of current granular carbon filters in adsorbing cytotoxics is not known. Concerns have also been expressed that particles released by such a carbon filter might be contaminated by the very substance that it is has removed from the air and that therefore a further HEPA filter is required. The performance with cytotoxics of a new type of carbon filter medium is currently being evaluated in a research project at the University of Bath. In the meantime it is recommended that all exhausts from cytotoxic isolators (and cabinets) should be ducted to atmosphere.

Interest in the use of isolators for the safe reconstitution of cytotoxic products is indeed awakening around the world and most purchasers are specifying negative isolators, if only to allay the not unreasonable fears of technicians who might be facing a career long exposure to these drugs of unknown toxicity.

1. Neiger J: Points to consider: Airborne microbial effect of in-leakage in a negative isolator. European Journal of Parenteral Sciences Volume 4 Number 3 1999
2. Clark C: Occupational exposure to cytotoxic drugs (Report on Seminar). The Pharmaceutical Journal Volume 263 1999

John Neiger is chairman and a founding director of Envair Limited, the leading independent manufacturer of biological safety cabinets and isolators in the United Kingdom. He sits on various standards committees including ISO TC 209 Working Group 7, which is writing the new standard for isolators (called separative enclosures). He has addressed numerous technical conferences around the world.