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Experience with Isolators in the UK

The first ten years

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By 1987 several UK hospital pharmacy centralised IV additive (CIVA) units and cytotoxic drug reconstitution units had invested in isolator technology. At this time the conflicting pressures of cost containment, expanding workload and the need to improve standards were beginning to emerge. Isolator technology seemed to offer a solution to these problems and isolators were marketed by the manufacturers as a means of avoiding the expense associated with the construction of conventional clean rooms.

The early isolators were classified as type I (operating under positive pressure) or type II (operating under negative pressure) and were available in rigid and flexible-film designs. A variety of different transfer hatch designs were employed, the most common having a flushing system in which air from the isolator workplace was vented through the inner transfer hatch door into the transfer hatch itself. This air was then vented out from the top of the hatch via a HEPA filter. At this time few transfer hatches were fitted with interlocks on the doors, let alone time delay systems. For larger scale operations and the preparation of TPN, "half-suit" isolators were introduced to give the operator mobility combined with a larger working area.

At first isolators were located in almost any area available, dispensaries, corridors, offices etc. Usually there was no control of the background environment or the air quality in the area where isolators were located. Another perceived advantage of isolators at that time was the avoidance of the need to wear clean-room clothing. Accordingly operators tended to wear their normal clothing or, at best, a white laboratory coat for working in the isolator.

During the first 2–3 years of isolator use in the UK there was very little thought given to maintenance and performance testing of isolators. Similarly, little attention was paid to leak testing, sterilisation and sanitation and to the monitoring of the environment inside the isolator.

Around the late 1980's – early 1990's there was increasing concern among quality control pharmacists and hospital pharmacists with a microbiological background that under such conditions the exclusion of microbiological contamination from products prepared in isolators could not be guaranteed, particularly in the case of the type II (negative pressure) devices. Gradually routine maintenance and performance testing was introduced. Isolator HEPA filters and seals were challenged with DOP and rudimentary leak tests based on the maintenance of an over- or under-pressure in the isolator for a given time period after the fan was switched off came into routine practice. Replacement of leaking, contaminated or damaged gloves became easier with the development of sleeve/cuff/glove systems to replace one piece gauntlets.

Microbiological monitoring of isolators also developed with settle plate and swab tests undertaken on, initially, a weekly basis. Sub-visual air particulate monitoring was undertaken on a monthly basis but because the early isolators had no sampling ports, the air sampling probe was introduced via the isolator sleeve which meant sacrificing a glove and risking the ingress of micro-organisms into the critical area. The generation of monitoring data highlighted deficiencies in the location of isolators and by 1990 it was recognised that isolators should be sited in a "controlled area" [1]. At the time this was considered to be a "socially clean" area for which only minimal gowning was required [1].

In 1993 isolator practice in the UK was influenced by a series of publications including:

a) The Design and Monitoring of Isolators: A Specification for Pharmaceutical Applications [2].
b) The Quality Assurance of Aseptic Preparation Service [3].

c) The Cytotoxics Handbook 2nd Edition [4].
d) Centralised Intravenous Additive Services Manual [5].

These documents collectively revised the use, monitoring and location of isolators in UK hospitals. However the most important document from the viewpoint of UK CIVA services and isolator users was published one year later. In April 1994 two children died at the Royal Manchester Children's Hospital because TPN feeds were contaminated by *enterobacter cloacae [6].* The source of contamination was traced to a filling tube, which as a disposable item should have been discarded after 24 hours use. However, the tube in question had been in position for 7 days and provided a reservoir of growth medium for micro-organisms which originated in the drain of a nearby sink. This incident was significant for many reasons, one of which was that the compounding of the affected TPN infusions took place in a positive pressure isolator. Although the isolator and its performance could not be implicated in any way [6], the incident raised the profile of isolator technology in a negative light. Since that time isolators have received unparalleled attention from the UK Medicines Control Agency.

As a result of the Manchester incident the guidance document Aseptic Dispensing for NHS Patients [7] was published (the so-called "Farwell Report"). This document emphasised the requirement for process validation and directed that "the principals of operation for isolators should be the same as for clean rooms" and the "transfer processes into the operational zones should be validated and appropriately monitored" [7]. In 1994 the "Isolators for Pharmaceutical Applications" [8] was published giving detailed and specific guidance to isolator users and manufacturers. Finally in 1997 the "Rules and Guidance for Pharmaceutical Manufacturers and Distributors" [9] re-inforced the need for validation of isolators and recommended that the background environment should be of at least EC Grade D. The above mentioned documents have shaped isolator practice and quality assurance into the standards seen today in UK hospitals. A comparison of practice in 1987 and 1997 is presented in *Box 1.*

Currently isolators are in widespread use in UK hospital pharmacy for the preparation of non-cytotoxic drugs (type I isolator) and cytotoxic drugs (type II isolator) in batch and non-batch processes. For larger scale batch processing of cytotoxic drugs used in out-patient dose banding schemes [10], gas sterilised isolators are becoming more popular. Initially used only in commercial compounding units, these devices enable the ingredients and components to be surface sterilised *in situ* thus reducing the risk of introducing microbiological contamination into the product. This type of process does present other challenges (for example ensuring that no sterilent gas enters the vial of ingredient drugs) and in the non-commercial hospital setting its use is restricted to a few centres.

Modern isolator design has enabled the development of quieter, les bulky devices which have improved ergonomics for operator comfort. Type II isolators used for cytotoxic work are externally ducted wherever possible (via at least one HEPA filter) and the exhaust is discharged at high level (above the building height). External ducting can present a problem when air extract rates are high (e. g. MDH Peteric isolator: 850 m^3hr^{-1}) because the air input into the clean room in which the isolator is located must be increased to compensate for this. A more satisfactory solution is to use one of the newer isolators with a lower extract rate (e. g. Medical Air Technology Isomat isolator: 180 m^3hr^{-1}).

Most of the isolators available today have independent pressure gauges for the work area and the transfer hatches. Many will have time-delays fitted to transfer hatch interlocks and often sampling ports will be fitted to enable access to each area of the isolator for air-particulate monitoring. Alarms will be fitted to warn of filter or pressure failure and in many cases HEPA filters can be changed without risk of exposure to entrapped cytotoxic drugs.

Following recent enforcement of Aseptic Dispensing for NHS Patients [7], the majority of isolators used for CIVA and cytotoxic work in the UK are located in a clean room of at least Class D standard which is accessed by staff through a two-stage changing procedure. In essence there is now no difference between the standard of clean room used to house a conventional laminar air-flow cabinet or an isolator.

Isolators are now routinely maintained (usually using external contracts with the manufacturers) and monitored *(see box 1).* All processes are validated and operators are trained in the use of isolators and in the processes carried out within them. After training, staff competency is assessed before staff are permitted to carry out work intended for administration to the patient. Although there is no evidence that a type II (negative pressure) isolator in an EC Grade D environment presents a risk of microbiological contamination, the UK Medicines Control Agency (MCA) have attempted to phase out the use of negative pressure isolators for cytotoxic work. However, UK pharmacists have published their concerns [11] that such a proposal would not guarantee the safety of staff working in the isolator from occupational exposure to genotoxic material.

In conclusion, the 10+ years experience of isolators in the UK has sometimes been

Dr Sewell graduated with a BPharm degreee from the University of Bath in 1979 and received his doctorate from the same University in 1982. In addition to his pharmaceutical qualifications he is also professionally qualified as a biologist and a chemist and is listed as a "Qualified Person" for pharmaceutical manufacturing and quality control. He held a senior post at the Regional Pharmacy Quality Control Laboratory in Bristol before moving to Exeter in 1985 where he was responsible for the centralised IV additive (CIVA) and cytotoxic reconstitution services together with quality control and production. In 1995 Dr Sewell moved to Plymouth where he holds a combined hospital/academic appointment as Pharmacy Research and Technical Services Manager and Reader in Biomedical Sciences. Dr Sewell first invested in isolator technology in 1986 and has since gained experience in the management and quality assurance of services using a variety of isolator technologies.

With an active research programme over the last 15 years Dr Sewell has around 100 publications of which many relate to oncology and cytotoxic drugs in areas such as clinical pharmacokinetics, drug stability/formulation, safe-handling and the use of audit to improve safety. He is a founding member of the International Society of Oncology Pharmacy Practitioners and is currently Chair of the Publications Committee for that Society. Dr Sewell is a contributing author to the Cytotoxics Handbook, a full member of the EORTC PAMM Group and is Associate Editor (Europe) for the Journal of Oncology Pharmacy Practice.

Box 1: Changes in UK Isolator Practice 1987–1997.

	Then (1987)	Now (1997)
Isolator design		
Alarm systems (pressure etc.)	No	Yes
Transfer door interlocks	No	Yes
Separate glove/sleeve systems	No	Yes
"Safe" change of HEPA filters	No	Yes
Isolator Location		
Dedicated clean room	No	Yes
Grade D standard or above	No	Yes
Access *via* changing rooms	No	Yes
Isolator Training/Validation		
Staff trained in isolator use	Sometimes	Yes
Competency assessment of staff	No	Yes
Broth transfer/fluorescent dye tests	Sometimes	Yes
Validated transfer of ingredients/components	No	Yes
Isolator Monitoring		
Daily pressure check	Yes	Yes
Daily leak check	No	Yes
Sessional finger-dab plates	No	Yes
Sessional settle plates	No	Yes
Weekly swabs/contact plates	Sometimes	Yes
Monthly particle counts	Yes	Yes
Monthly microbial sampling	No	Yes
Six monthly DOP test	Sometimes	Yes
Isolator Practice		
Full SOP's	No	Yes
Clean room clothing used?	No	Yes
Validated sanitisation process and records	No	Yes
External maintenance contract	Sometimes	Yes

painful as use of this technology has evolved. However, advances in the technology, ergonomics and quality assurance of isolators have given isolators widespread acceptance among hospital pharmacists, particularly for cytotoxic reconstitution work.

References

[1] The Cytotoxics Handbook, 1st Edition. Eds. M. Allwood and P. Wright, (1990) Radcliffe Medical Press, Oxford.

[2] The Design and Monitoring of Isolators: A Specification for Pharmaceutical Applications: Regional QC Sub-Committee (1993), London.

[3] The Quality Assurance of Aseptic Preparation Services: Regional QC Sub-Committee (1993), London.

[4] The Cytotoxic Handbook, 2nd Edition. Eds.: M. Allwood and P. Wright, (1993) Radcliffe Medical Press, Oxford.

[5] Centralised Intravenous Additive Services Manual: National CIVAS Group (1993), London.

[6] Anon. Two children die after receiving infected TPN solutions. Pharmaceutical Journal (1994) *252*, 596.

[7] Aseptic Dispensing for NHS Patients: Department of Health (1994), London.

[8] Isolators for Pharmaceutical Applications Eds.: M. G. Lee and B. Midcalf. HMSO (1994), London.

[9] Rules and Guidance for Pharmaceutical Manufacture and Distribution 1997. Medicines Control Agency, the Stationary Office, London.

[10] Baker J. P. and Jones S. E. Rationalisation of chemotherapy services in the University Hospital Birmingham NHS Trust. Journal of Oncology Pharmacy Practice (1998) 4 (1) 10–14.

[11] Needle, R., Sewell G. J., Summerhayes M. CIVA Services. Hospital Pharmacist (1998). In Press.

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