Case Study: The Selection and Evaluation of an Isolator System Required for Rapid Response Pharmaceutical Compounding.

aseptic
technology & design

Case Study: The Selection and Evaluation of an Isolator System Required for Rapid Response Pharmaceutical Compounding.

(Abstract of a paper presented at the 8th Pharmaceutical Isolator Conference, Warwick 2004 and the ISPE Barrier Isolation Technology Forum, Prague 2005)

Dr. Brian Bergin (Aseptic Technology & Design Ltd) and Michael Greenbank (Baxter Healthcare UK Ltd)

Hospital pharmacy aseptic compounding units are under increasing pressure to deliver more, of better, for less. 'More' because the expectation for healthcare provision is to increase patient throughput and drive down waiting and treatment times. 'Of better' because the regulatory bar is ever rising. 'For less' in order to reduce treatment cost per patient. Realistically, in the area of aseptic compounding, the only hope of meeting such demands is by investment in new technology. With a large investment project comes difficult decision-making. Indeed, capital proposals must include a sound business case and withstand close commercial scrutiny. Then finally comes the most difficult part - project and operational performance delivery.

Another option is to outsource aseptic compounding activities to a service provider who already has the necessary skills, technology, infrastructure and ability to deliver the requirements of the healthcare provider.

Baxter Healthcare provides aseptic compounding services to the highest standards from 4 UK units. Chemotherapy, antibiotics, antivirals, and parenteral nutrition admixtures are prepared under aseptic conditions using specialist equipment, and delivered to hospital pharmacists. This service reduces the pressure on hospital pharmacies and increases potential patient throughput. Baxter has over 15 years expertise in aseptic manufacture and significant experience in assisting with the establishment of Pharmacy Services. It has recently invested in a new pharmacy compounding facility in the Northwest of England that will serve many hospitals including the Christie.

This paper details the decisions taken in choosing and specifying 'State of the Art' fully integrated isolator equipment for the new facility. This paper will describe how the application of 'value added' analysis can help to focus process effort on key deliverables and demonstrate how an integrated isolator system can achieve significant improvements in process efficiency. This paper clearly shows the importance of understanding the requirements of the healthcare provider and translating these into a detailed User Requirement Specification (URS) to determine the design of the equipment. Where groundbreaking techniques are to be used, the building and thorough testing of equipment prototypes is shown to enhance the decision-making process and safeguard project timelines and budgets. The new equipment utilises rapid gassing technology thus guaranteeing a high sterility assurance level of its dispensed products with processing times that are significantly faster than those achieved by using traditional aseptic techniques.

Project Background

With this project Baxter Healthcare wanted to address a number of issues, common to anyone using isolators for aseptic compounding. Traditionally, peracetic acid has been used as the sanitizing agent for simple pharmacy isolators and Baxter was clear that they wanted to move away from this. However, previous experience with hydrogen peroxide had led to very long gassing cycles, which in the event of equipment failure or breach of the aseptic environment meant long and expensive recovery times. Aseptic Technology & Design Ltd (ATD) were therefore commissioned to review Baxter's existing processes and make recommendations for improvements based on their extensive knowledge of isolator technology and aseptic manufacturing.

Existing Process

The aseptic connections and manipulations required to achieve dispensing of pharmaceutical prescriptions were undertaken within the controlled environment of a sanitisable barrier system or isolator, designed to eliminate direct operator contact with the sanitised equipment and the dispensing process. Non-direct operator interaction with the process was through glove ports and/or half suits. The process flow is depicted in Figure 1 and briefly described overleaf.

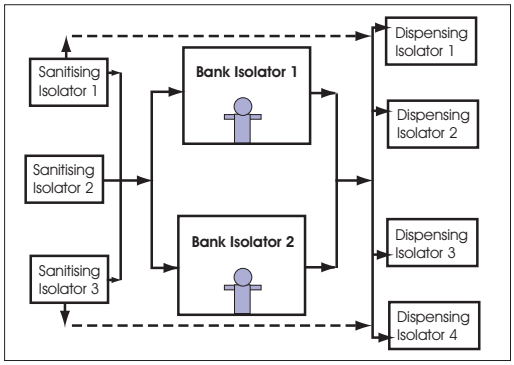


Figure 1: Existing Process Flow Diagram

aseptic technology & design

6 Stocks Fold, Old Hall Lane, East Markham, Nottinghamshire, NG22 0RF.
Tel/Fax: +44 (0)1777 872 639 email: admin@aseptic.com

Bulk prescription components were obtained from storage and loaded into one of three 'sanitising' isolators. A sanitisation cycle was then initiated to effect the surface decontamination of the components using peracetic acid or Vapour Phase Hydrogen Peroxide (VPHP). On completion of the cycle the components were transferred using sealed Rapid Transfer Port (RTP) canisters to one of two 'bank' isolators to be held as work-in-progress awaiting picking. It was also possible to transfer components direct to any one of the four dispensing isolators. Direct transfer to dispensing isolators was much less frequent, as it depended on the correct components being available from the sanitising isolator load, at the same time as they were needed in the dispensing isolator.

Components required for dispensing were selected from the bank isolator and transferred again using sealed RTP canisters into one of the four dispensing isolators where the prescription(s) was made up. The completed prescription and any waste generated were passed out of the dispensing isolator via a Rapid Transfer Port (RTP) pass out sleeve, which was attached to the side (end wall) of the isolator.

Whilst the existing 'bank' process enabled Baxter to provide a compounding service, this way of working proved to be unreliable and any breaches or compromise of the aseptic environment created extremely long and expensive recovery times. This was because the sanitising isolator/gas generator combination exhibited long cycle times, which meant it would take approximately one week to completely re-stock the 'bank' isolators.

The weaknesses of such a process flow are many-fold (see table 1) but crucially for the healthcare provider and patient, it is difficult to respond to emergencies and sudden changes in requirements. The process was clearly very inflexible.

Value Added Analysis

A 'value added' analysis of the process (Table 1) highlighted the disproportionate level of support activities required to dispense prescriptions. Support activities were time consuming, required high maintenance and control, consumed additional resource and ultimately provided little flexibility. The key to radically improving the existing process was to eliminate as many support and non-value adding activities as possible. Attention was paid primarily to reducing the operational effort deployed in running the sanitising and bank isolators.

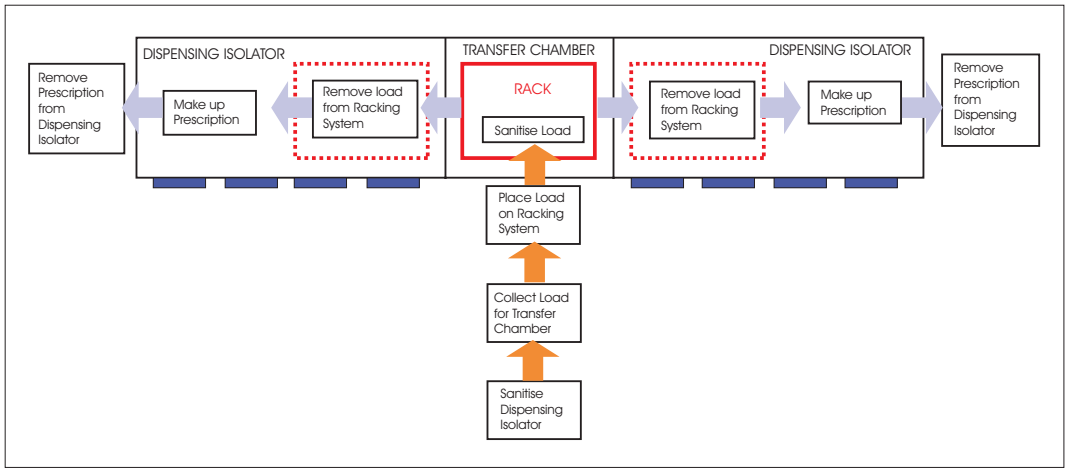


Figure 2: Rapid Gassing Chamber Process Flow Diagram.

By carrying out this analysis ATD were able to propose several integrated isolator concepts that would significantly reduce the number of support activities involved and at the same time provide a more efficient and flexible operation. ATD had successfully developed a rapid transfer chamber system with Metall + Plastic GmbH (Radolfzell, Germany) for the aseptic transfer of syringe tubs into an isolator using hydrogen peroxide. This system, which was installed at Solvay Pharmaceuticals (The Netherlands) in 2001, had a decontamination cycle capable of achieving a 6-log spore reduction in only 12 minutes. It was realised that if prescription components could be sanitised in such a chamber, in sufficient quantity, in a similar time, the sanitising and bank isolators could be eliminated. The concept that was presented to Baxter is shown in Figure 2.

A 'value added' analysis of the proposed rapid gassing process (Table 2) clearly demonstrated a significant reduction in the number of support activities and associated equipment. The rapid gassing concept was thus identified as the preferred option for the new equipment.

Prototype Evaluation and Equipment Selection

Whilst the advantages of the rapid gassing process were very attractive, the performance of such a system in terms of decontamination time for compounding

Table One

Step No.	Process Step	Advantages	Disadvantages	Activity
1	Collect full standard load for one of three Sterilising Isolators (SI)	Redundancy of SI's in case of failure	- Capital investment, validation costs, maintenance costs	*Support*
2	Set up the standard load for gassing.	Minimised validation costs as only one load to validate	- Only one load configuration. No flexibility - Gassing stock that is not needed - How is re-gassing of extra stock from the bank controlled? - Time consuming (1 hour) due to lack of access to the isolator	*Support*
3	Sanitise standard load		- Manual intervention required to ensure gloves sanitised - Long cycle times	*Support*
4	Unload complete contents into bank using DPTE's		- Time consuming (1 hour) - Increased contamination risk to bank and load - Bank occupied during this period Increased number of DPTE's required - Sterile/non sterile DPTE's need to be tracked -risk of contamination/errors - Fixed load being transferred to bank may not match actual usage of product leading to unwanted extra stock in bank therefore more space required	*Support*
5	Product awaits picking in bank	1. Sterilised product is ready & available for immediate picking if bank not in use. 2. Possibility of returning part used containers for storage in sterile environment.	- Leaks in isolator may render product unusable until re-sterilised - High capital cost - Takes up significant floor space - Poor utilisation of space in bank due to storage system and half suit	*Support*
6	Pick pescription from bank	Product available sterilised at short notice if bank avail.	- Time consuming if bank in use - Increased contamination risk to bank and load - Bank ocupied during this period - Increased number of DPTE's - Sterile/non sterile DPTE's need to tracked -risk of contamination/errors - Usage of product leading to unwanted extra stock in bank therefore more space required - An additional inventory which needs to be controlled (Merlin) - Fridge needs to be accommodated in a grade A zone	*Support*
7	Transfer to Dispensing isolator (DI)	None	- Additional transfer risk to DI and bank - Weight of load can be restrictive - Control of DPTE's	*Support*
8	Sanitise DI	None	- Long cycle time with current VHP experience	*Support*
9	Remove prescription from DPTE	None	None	*Support*
10	Make up prescription	None	None	*VALUE ADDING*
11	Remove prescription from DPTE	None	- Cost of consumables i.e. sleeves - Risk of puncture	*Support*

Table Two

Step No.	Process Step	Advantages	Disadvantages	Activity
1	Collect load for Chamber	1. Sterilising isolators not required 2. Bank not required	- Sterile stock not available immediately	*Support*
2	Set up the load for gassing	1. Flexible, only stock that is needed is gassed 2. Re-gassing of stock is eliminated	- Increased validation of load configurations	*Support*
3	Sanitise flexible load	1. Automated rapid cycle	- None	*Support*
4	Unload components into DI	1. Quick transfer 2. Half suit not required 3. DPTE's not required hence less risks 4. No build up of stock 5. Bank not required	- None	*Support*
5	Sanitise DI	DI to be sanitised via chamber system	- None	*Support*
6	Make up prescription from DI	None	- None	*VALUE ADDING*
7	Remove prescription from DI	1. Unloading into Chamber 2. No consumable Costs 3. No time wasted loading sleeve	- None	*Support*

aseptic technology & design

6 Stocks Fold, Old Hall Lane, East Markham, Nottinghamshire, NG22 0RF.
Tel/Fax: +44 (0)1777 872 639 email: admin@aseptd.com

components had not been proven. This was new technology to Baxter and in order to reduce business risk and build confidence in the feasibility of the system, ATD suggested the inclusion of two distinct phases in the URS. Phase one involved the design, fabrication and development of a prototype Component Transfer Chamber (CTC) system (approx 0.5m3 internal volume) that would be used to assess performance before moving to phase two. Phase two was the project proper including the supply of a number of compounding isolator systems.

Evaluation criteria for the prototype CTC were determined by collating details of the range of components and materials that would need to be accommodated by the chamber. The existing product mix delivered to customers was analysed in order to establish trends and similarities of workload. The mix and quantity of components required to make up 1-2 hours dispensing was determined in order to define the capacity of the racking system required to support the components and materials being transferred. This data was then used to define a number of different loads for the testing and validation of the prototype CTC and

Figure 3

incorporated into the URS. The test loads would have to be surface decontaminated and the CTC aerated to less than 1ppm hydrogen peroxide in less than 15 minutes. In order to prove this, the decontamination process would be challenged with Tyvek-wrapped biological indicators each loaded with greater than six-logs of *Geobacillus stearothermophilus*.
The URS was distributed to several isolator manufacturers and two VHP Generator suppliers. After the initial tender phase, two suppliers were chosen to proceed with the manufacture of a prototype CTC system for evaluation. Following discussions with Baxter and ATD the chosen suppliers designed and fabricated the prototype chamber and provided all the necessary equipment to enable Baxter and ATD to test the suitability and effectiveness of the system and the sanitisation cycle. The testing took place at the supplier's facilities.

Phase Two Evaluation Criteria

In addition to the satisfactory completion of the prototype testing, the choice of supplier progressing to phase two was also dependant on a detailed assessment of the proposed equipment. Phase two required 4-glove dispensing isolators with the option to integrate or connect the chosen CTC. It was a requirement that the sanitisation cycle of the isolators would be complete in < 4 hours (including aeration to <1ppm). Metall + Plastic (M+P) were the only manufacturer to meet the evaluation criteria for phase one and were therefore chosen as the preferred supplier. The following section defines the evaluation criteria used to select the preferred supplier and provides some insight into the decision to progress with the M+P system. The final as built system is shown in figure 3.

Capital and Operational Costs

An important factor when considering capital costs is to also include an estimation of the operating and maintenance costs over the anticipated lifetime of the equipment. The capacity of the M+P chamber meant it could accommodate up to three hours workload and thus minimize the actual number of transfers required. This was an important factor when considering liquid hydrogen peroxide consumption which over several years can provide a significant cost saving. There was no significant difference between the capital costs of the M+P equipment compared to the other equipment under evaluation. The adoption of the rapid gassing concept meant that capital costs were significantly lower than would have been the case using the 'bank' system.

Production Requirements/Suitability

The requirements for production considered not only the performance of the CTC in providing rapid gassing of components but also the various procedures involved in operating the chamber in an easy and safe manner that would provide a validatable, robust and reliable process.

Capacity

The dimensions of the prototype rack was 600mm(L) x 600mm(H) x 600mm(W) giving a load space capacity of 0.22 cubic metres, 60 percent of the overall chamber capacity. The prototype chamber had enough capacity to supply two Dispensing Isolators and sufficient capacity for the dispensing of Total Parenteral Nutrition (TPN) components.

Cycle Time

The requirement was for the chamber to achieve a minimum 6-log reduction of bio-burden of all surfaces within 20 minutes. It was demonstrated that the 6-log cycle including aeration to less than 1ppm of hydrogen peroxide was achievable in less than 12 minutes. The data gathered was consistent for 9 different load configurations.

The rack was made from stainless steel and built onto four bi-directional wheels meaning the rack was a free standing structure that was easily manoeuvrable back-and-forth and side-to-side. There were several operational advantages to this approach: As the rack was free standing, it could be loaded away from the

6 Stocks Fold, Old Hall Lane, East Markham, Nottinghamshire, NG22 0RF.
Tel/Fax: +44 (0)1777 872 639 email: admin@aseptd.com

isolators and dispensers in a loading area within the clean room or in a separate 'prep' room.

Having the prepping and loading away from the isolators and other operators reduced the Health & Safety risks to the clean room staff. Loading in the prep area eliminates double handling of components making the process more efficient. The loaded racks can simply be wheeled from the prep area straight to the relevant chamber.

During times of high demand and peak activity where a series of rapid response doses are required, the rack can be pulled into one isolator freeing up the chamber immediately for loading with the next rack.

Ease of Loading/Unloading

The chamber and rack is not loaded through a door or opening which could restrict operator access.

Different racks can be designed to suit the product type and mix for each workstation. This allows maximization of the capacity of the chamber for TPN, chemotherapy, etc.

The entire rack can be unloaded into the dispensing isolators after gassing making unloading easier.

Operator Interface

It was a requirement to minimize operator input required for correct operation of the equipment. The M+P system was controlled from a single operating panel at which all aspects of operation including sanitization were initiated. It was specified that there should be no manual connections prior to gassing cycles. As the gas generator was fully integrated with the system, no manual connections were required and the number of manual checks and documentation in operation is thus reduced. Another important feature was the absence of the requirement to manually handle and weigh the liquid hydrogen peroxide.

Cleaning

Full access to all areas of the chamber for cleaning was required without compromising the sterile status of the attached isolators. The component rack was not a permanent feature of the chamber and could be completely removed for cleaning of both. All doors could be interlocked and linked to the "sterile/non-sterile" status of the attached isolators. There were no occluded areas or "telescopic" components that might harbour a build up of debris or toxic powders. Unlike a telescopic system, cleaning of the chamber and rack could take place whilst both attached isolator systems remained 'sterile'.

Contingency

In the event of generator breakdown it was a requirement that the system must have built in contingency. The prototype chamber was capable of providing unidirectional down flow at a flow rate of 0.45m/s. This enabled the chamber to be used as an ISO 5 pass-through hatch. The M+P equipment is also provided with a built in modem for remote diagnosis and fault clearing thus minimising downtime.

Disaster Recovery

In the event of a compromise of the aseptic environment it was a requirement that the complete isolator system could be opened, cleaned and gas sanitized ready for production in less than 4 hours. M+P provided evidence that isolators of a similar size could be sanitized in 2-3 hours.

Quality & Reliability

Preference was given to suppliers able to demonstrate experience in the design and build of fully integrated systems. M+P had a proven history in isolator and transfer chamber design and manufacture.

Integrated Isolator Module

After careful consideration and detailed evaluations of the available systems, Baxter invested in three fully integrated Isolator Modules manufactured and installed by M+P. A second URS was drafted to incorporate the requirements of an integrated isolator module. Each module was broken down into the following main equipment items:

1 x Transfer Chamber
1 x Racking System
2 x 4-Glove Dispensing Isolators
1 x VHP Generator

The modules were fully tested at a Factory Acceptance Test (FAT) in order to ensure that before the equipment left the factory that there were no outstanding issues. This was a major factor in assuring that the project was delivered on time and within budget. The importance of the FAT should not be under estimated. All aspects of the sanitisation cycles were tested to ensure that the performance of the module was equivalent to the performance of the evaluated prototype.

As Built Equipment Performance

The CTC achieves a 10-log reduction of *G. stearothermophilus* at all locations with a cycle time (including aeration to <1ppm) of <15 minutes. The system guarantees a high level of sterility assurance for dispensed products with processing times that are significantly faster than those achieved by using traditional 'spray and pray' techniques. Variable load configurations have been tested and have no effect on cycle times or capability. This allows greater flexibility as the process is not restricted by fixed load configurations.

The attached dispensing isolators may be sanitised together or independently with a cycle time of < 1 hour (including aeration to <1ppm). This is a major process improvement and allows for rapid recovery in the event of a compromise of the aseptic environment.

The preparation of a newly ordered dose of chemotherapy follows the process description below.

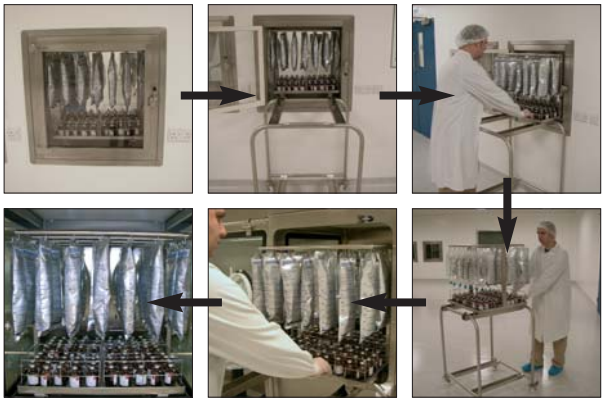
6 Stocks Fold, Old Hall Lane, East Markham, Nottinghamshire, NG22 0RF.
Tel/Fax: +44 (0)1777 872 639 email: admin@aseptd.com

1. An order is received and entered onto Baxter's Merlin inventory control and tracking system for review and allocation to one of the dispensing isolators.

2. The operator working in the dispensing isolator runs an inventory pick for his/her location on the Merlin system and a picking list for all of the required components is generated in the prep area.

3. The components are assembled from the stores/prep area, prepped and then loaded onto a rack in the prep area keeping the prepping and loading activities out of the clean room and away from the dispensers. The loaded rack is then passed through a hatch onto a trolley in the clean room. The prepping work surfaces and hatches within the prepping area is built to the same height as the clean room trolleys and chamber/isolator bases to allow the racks to be moved from one work surface to the next with ease.

4. The trolley is wheeled to the relevant chamber where the rack can be simply pushed directly into the chamber and the door closed.

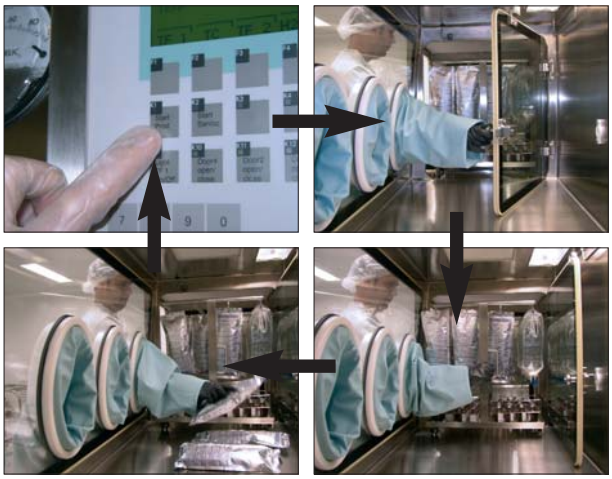


5. Each chamber has its own control panel mounted on the chamber front and on the push of a button, the door is pneumatically sealed and the cycle is initiated.

6. On completion of the sanitization cycle, the interlocked doors to the isolators are released and the rack can be wheeled from the chamber into one of the dispensing isolators.

a. The racks are drawn completely into the dispensing isolators easing the unloading process for the operators. The racks can be manoeuvred within the isolator to the position most comfortable for the dispenser working in that workstation.

b. If the rack contains components for both attached isolators then it can be simply pushed through the chamber from one isolator to the next once unloading for isolator 1 is complete.



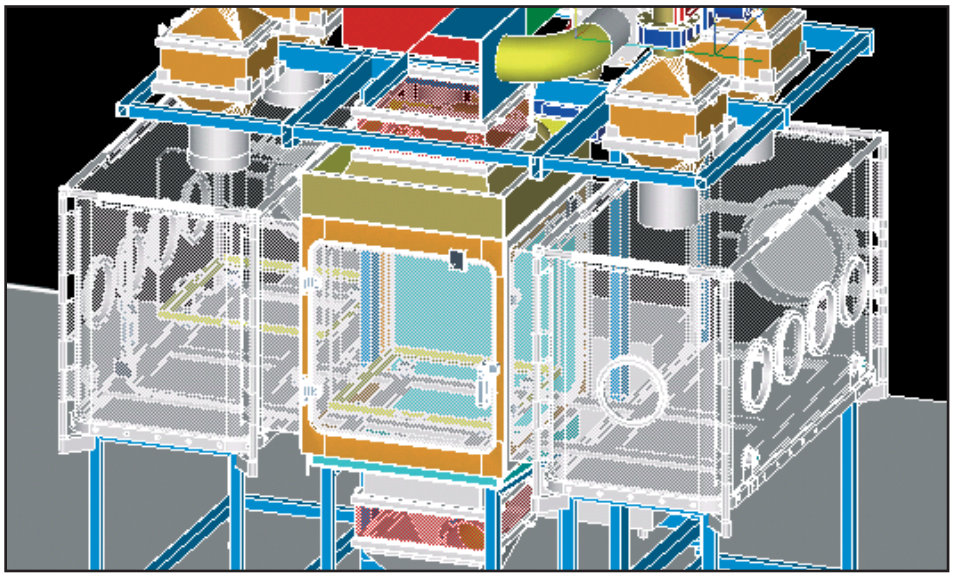
7. Once unloaded, the racks are passed back into the chamber for re-use and the door from the isolator to the chamber is closed and pneumatically sealed.

8. The door from the chamber to the clean room can now be opened and the rack removed. The chamber is ready for re-use.

Conclusion

This project was delivered on time and under budget and was a major success for Baxter Healthcare. Careful definition of customer requirements up front, allows the equipment to be designed to deliver the optimum process. The building and testing of prototypes and independent evaluation of the sanitisation capabilities of the equipment before buying, allowed Baxter to make an informed equipment choice and drastically reduced the potential business risk of investing in a new technology. Rapid gassing technology developed by ATD in association with M+P has revolutionized the compounding pharmacy operation.

Integrated isolator systems make **RAPID RESPONSE** compounding services a **REALITY** for the first time.



For further information please contact:
admin@aseptd.com
Tel/Fax: +44 (0)1777 872 639

or write to us at:
Aseptic Technology & Design Ltd
6 Stocks Fold,
Old Hall Lane,
East Markham,
Nottinghamshire,
NG22 0RF.
UK.