A history of isolator and containment technology Part 2: Flexible film isolators

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Abstract

This is the second of five papers that will describe the history and development of isolator and containment technology in the fields of research, medicine and pharmaceutical applications.

The paper commences with the development of flexible film isolators based on designs similar to Trexler's later models and the expansion of the use of such isolator designs by the pharmaceutical industry into sterility testing, aseptic processing and, in containment format, for compounding hazardous products. Hospital pharmacies also picked up the technology for dispensing.

Flexible film isolators

With the introduction of flexible film isolators by Trexler in the USA, and the UK interest in such isolators, the technology developed further. In the USA a small number of companies produced similar Trexler isolators for gnotobiotic animal rearing and research, but at that time there was a limited market and the number of manufacturers dwindled down to two or three. One of these was Standard Safety Inc.

However there was much interest in using isolators for developing biological warfare agents and the business expanded in that direction in both the USA and the UK.

La Calhene (now Getinge- La Calhene) in France also developed flexible film isolators for germ-free rodent breeders for animal research. These were similar in design to the Standard Safety models from the USA.

Another application for flexible film isolators at that time was for surgical procedures such as hip joint replacement. The unit had several glove ports and an RTP. The flexible floor of the isolator had an adhesive outside surface (suitably protected before use.) The isolator was placed over the operation area of the patient, the protective sheet was removed from the adhesive and the floor of the isolator was fixed to the skin of the patient over a fairly large area.

The surgeon incised through the plastic and the skin at the same time. It is to be noted that the isolator had been previously decontaminated.

La Calhene's original work was in the field of containment for the French nuclear industry (CEA-French Atomic Energy Board) commencing in 1960. They made PVC bags for waste materials, remote handling systems (mechanical arms and hands) and a flexible glove box for hazardous materials. In collaboration with CEA they also co-patented the DPTE® (double porte de transfert étanche) now more commonly known as an RTP (rapid transfer port). DPTEs® and RTPs plus other types of transfer chamber which will be discussed in a paper later in this series.

La Calhene also built several isolator systems for immuno-compromised patients in France similar to the unit

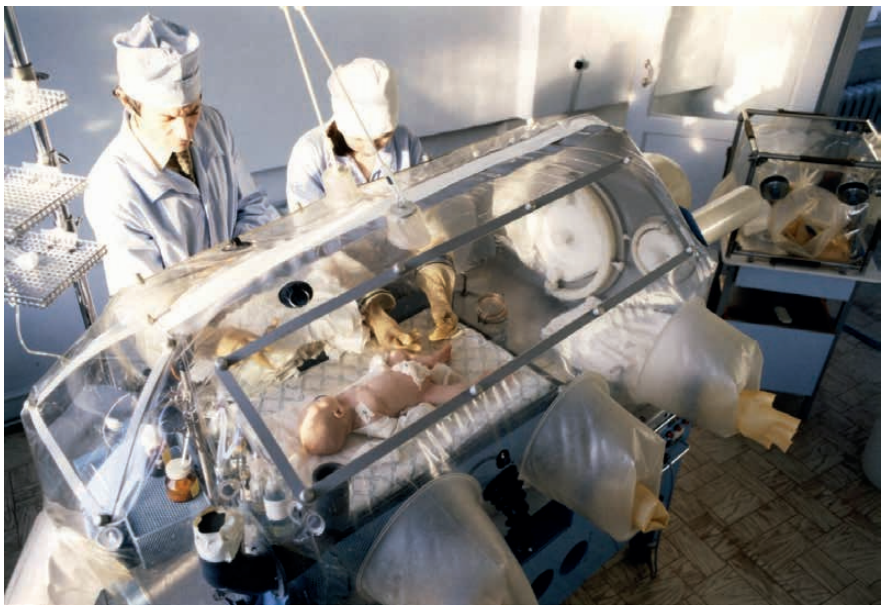

Figure 1: Baby in an early La Calhene isolator (attended by parents)

Figure 2: A La Calhene sterility test isolator circa 1980

described in the previous paper of this series. One example, for a baby, shown in Figure 1, closely resembles one of Trexler's models.

The company continued to expand their range of isolators for animal research and hospital use and, at that time, they were all equipped with canister type HEPA filters and one blower.

Interest from the pharmaceutical industry initiated the development of flexible film sterility test isolators. The first of these, shown in Figure 2, was built circa 1980 and may well have been one of the very first flexible film isolators used for that purpose. Two later innovations were the half-suit isolator and a free-standing automatic peracetic acid vapour generator.

The early La Calhene isolators stood on a plastic coated table. The isolator had a transparent canopy of PVC with a grey plastic floor. The plastic canopy was supported on a metal tubular frame. Above the frame was a plastic covered board on which were fixed the blower, the filters and an inclined tube manometer for measuring pressure inside the isolator. Pressure was controlled by adjusting the speed of the blower. A T-junction on the input air pipe allowed for the connection of a peracetic acid gassing device.

Large glove-rings were fixed onto the PVC canopy with metal worm-drive clamping bands and glove sleeves were fitted securely to these with rubber O-rings. Materials entered and exited the isolator via a DPTE® or via a circular opening with a cover that could be removed. Later models had the floor replaced with a stainless steel base to which the PVC canopy was fixed in a leak free manner.

The distance that can be comfortably reached via a standard sleeve and glove arrangement is about 800 mm, dependant on the size of the operator, but, as the size of the isolators increased, as well as the desire to perform more complex manipulations, La Calhene offered their half-suit design as shown in Figure 3.

This was double skinned and sealed at waist level onto an oval ring set in the base of the isolator. It was equipped with a blower and a HEPA filter to provide respiratory air to the operator's face and arms. This air entered via the space in the double skin, blew into the transparent head cover and the wrist area and left via the inside of the suit back to the room. The half-suit was entered from beneath the isolator and the floor of the isolator at that point was usually set at a slight angle to aid entry.

This in essence is the basic isolator design that subsequent manufacturers developed with slight variations for sterility testing purposes and for further-germ free animal breeding and research.

The use of isolators for sterility testing started to slowly expand in the late 1980s into the early 1990s, mainly in Europe, but in 1993/1994 the USP (United States Pharmacopeia) changed the criteria for a failed sterility test. The result was a surge in the use of isolators for sterility testing in the USA and in Europe in a variety of systems that ensured maintenance of sterility.

A few of the larger pharmaceutical companies used isolators attached to an autoclave to maintain the external sterility of the media tubes or bottles. These were transferred into the sterility test isolator via a DPTE®. When the tests were completed, the media tubes were placed into a small transfer isolator, again by a DPTE® port. The transfer isolator was then placed into an incubator room. Thus the media tubes were never exposed to the external environment or to the operators performing the tests. This set-up was aimed at eliminating the possibility of false positive growth results.

Other examples of flexible film isolators are seen in Figures 4 and 5.

At this time Amsco (now Steris Corporation) had been developing hydrogen peroxide vapour decontamination technology and had produced a hydrogen peroxide gas generator for use with isolators. They also started to market an isolator system called Oasis for sterility testing. These models were designed and manufactured by La Calhene and again featured the DPTE® device.

Parallel with this activity, Millipore, who had supplied filtration systems for sterility testing (the open cup method), developed a closed system with a piece of equipment that would fit onto the base of a sterility test isolator (Steritest™).

There are now in excess of over 700 sterility test isolators throughout the world and only a very small number of sterility test failures have been recorded. These were found to be due to human error[i]. This demonstrates the high degree of assurance in using isolator technology plus the security of the DPTE® system. An example of the latest version from Getinge- La Calhene (Isoflex) is seen in Figures 6 and 7.

Figure 3: La Calhene half-suit (demi-scaphandre)

Figure 4: Typical simple flexible film isolator – Class Biologically Clean Ltd, USA

Figure 5: Typical half-suit flexible film Isolator – Pharminox Isolation Limited, UK

There was also a full suit (scaphandre) design (see Figures 8, 9 and 10). This incorporated a special DPTE® for entering the suit (see Figure 9). Clearly the diameter of the opening placed a limit on the size of operator who could use the suit. The application was in certain sterile areas such as the loading and unloading of freeze dryers.

Other types of full suit protection were developed in the USA during the period of research into and manufacture of biological weapons as depicted in Figure 11. Such types of suit are now in use during the study and identification of highly contagious microorganisms within a Level 4 biological containment environment (Figure 12).

Flexible film isolators for germ free animals and for veterinary use continued to expand in Europe and also in the USA through the development of companies dedicated to breeding such animals for research purposes and Trexler played a role in the development of two of these companies. They continue to provide gnotobiotic animals today.

Metall + Plastic in Germany produced flexible film isolators on a grand scale. One design had a vertical rotating cage system for germ free animals set inside a very tall polyurethane plastic canopy, about 7 meters high. The design used electric motors and a star-wheel/chain system to rotate the system in order to bring one cage at a time down to the front of the operator. He or she could then perform cleaning and feeding operations through a set of gloves without having to enter the enclosure.

Figure 6: Isoflex flexible film sterility test isolator – Getinge- La Calhene

Figure 7: The Isoflex seen from the inside

Metall + Plastic also developed doors with expanding seals for stainless steel chambers where peracetic acid was sprayed into the chamber. This technique was used to decontaminate the exterior of metal containers holding sterile antibiotic raw materials. (Peracetic acid and other chemicals used to decontaminate isolators will be discussed in a later paper in this series).

Flexible film isolators were also adopted in hospitals in certain parts of Europe, notably in the UK and in France. One example is shown in Figure 13. There was a requirement to compound or mix sterile drugs under aseptic conditions and this was being carried out in traditional open fronted safety cabinets. There were concerns regarding sterility assurance as well as operator safety when compounding certain drugs such as antibiotics and cytotoxics. One result was a guideline published in the UK in 1994 with regard to procedures, quality control and quality assurance[ii]. This was completely rewritten in 2004 as an authoritative book on the subject[iii]. Crauste-Manciet[iv] gives a good description of the requirements for high volume preparation in hospital.

Following on the success of the use of flexible film isolators there was a rapid expansion of suppliers of these types of units. They were (and are) based on the original Trexler concept but airflow systems have become more sophisticated with larger rectangular HEPA filters replacing the cartridge HEPA filters where higher air change rates and unidirectional airflow are required.

Isolator designs also evolved from Cambridge Isolation Technology in the UK (now Pharminox Isolation Ltd). Pharminox continues to make sterility test isolators but also supplies half-suits, RTPs, gloves and sleeves for isolators and other isolator components.

Other manufacturers also followed including Amercare, Bassaire, Bell, Bioquell, Contained Air Solutions,

Figure 8: Entering an isolator via a Scalhene full suit

Figure 9: Arriving in the isolator in a Scalhene full suit

Figure 10: Inside the isolator in a Scalhene full suit

Envair, Extract Technology, Hosokawa Micron, Howorth Air Technology, Mach-Aire and Powder Systems in the UK. Non-UK suppliers include Skan AG, Telstar, Metall + Plastic, Bosch and Steriline. This list is far from exhaustive.

The pharmaceutical industry had seen the various designs and techniques used for germ free animals, containment for immune compromised patients, etc., that demonstrated the possibility of working in a controlled environment with a high degree of confidence in maintaining sterility. The use of positive pressure was seen as an essential way to maintain an aseptic or sterile environment inside the isolator.

It was also found that the methods and agents used to decontaminate animal isolators could be used in the pharmaceutical industry for sterility testing on the one hand and for improved aseptic filling on the other.

In the search to improve testing and manufacturing environments in the pharmaceutical industry in the 1980s, it was found that the methods and agents used to decontaminate animal isolators could be used. In addition, the use of containment techniques for the containment of highly potent or hazardous materials that had to be compounded into a finished pharmaceutical product was being explored. The positive-negative debate is still there in the background but, to put it into perspective, all isolators, being total enclosures, provide both an aseptic environment and containment. The problem arises if there is any leakage of contaminated air in or out. Therefore, where aseptic conditions are the predominant requirement, then

Figure 11: Full suits, USA

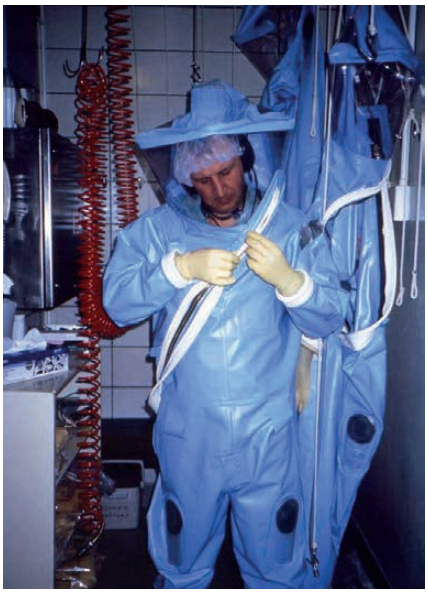

Figure 12: Biological safety suit at CDC (Centers for Disease Control and Prevention), USA

Figure 13: Simple pharmacy isolator – Flexipharm from Extract Technology

positive pressure isolators are favoured and where containment is the predominant requirement, then negative pressure isolators are favoured.

It is fair to say that the regulatory authorities, such as the MHRA, prefer positive pressure isolators and the safety authorities, such as the HSE, prefer negative. However, having said that there are positive pressure flexible film isolators in use that handle cytotoxic drugs and their use will have been subject to proper risk assessments.

The first pharmaceutical manufacturing unit in an isolator system was by Farmitalia in 1978. The unit was produced by La Calhene. This was a powder filling operation and the unit was fitted with quite a number of gloves. It is believed that this unit was the first to use a rapid transfer port (DPTE®) outside of the nuclear industry.

La Calhene, in the late 1980s also made an isolator to surround an ampoule filling line in France. This unit was mainly flexible film with appropriate metal areas for exhausting the hot air from the flame sealing of the ampoules.

A further development from La Calhene was a Spanish facility using a flexible film isolator for filling large volume parenterals. This involved a small railway system for moving trolleys of sterile bottles from an attached autoclave to the filling position.

The decontamination of the unit was performed from a STAR peracetic acid unit, also made by La Calhene. Over the years this unit has been developed further and is now marketed under the name of ISOVAP.

In the 1990s, a company in south-west France built a system to compound and aseptically fill cytotoxic products. The filling line incorporated a dry heat vial depyrogenation oven which was attached to a filler. The line progressed to a freeze drier, then onto a capper and finally to a washer for cleaning the exterior of the filled and capped vials. The entire line was enclosed with an isolator system made of stainless steel. Flexible film isolators were used to transfer sterilized items from an autoclave to various of the isolator units. The compounding of the product was performed in a negative pressure isolator and the required testing for batch release was performed in another isolator.

The entire system excepting the dry heat oven and the body of the freeze dryer was all in one large room[v]. This type of isolator use has now been expanded by other companies and in the next paper in this series a history the use of metal and rigid plastic isolators will be presented.

i. Personal communication from James Akers of Akers Kennedy Inc, USA.

ii. Isolators for Pharmaceutical Applications, Edited by Gerard Lee and Brian Midcalf, HMSO, 1994.

iii. Pharmaceutical Isolators: A Guide to their Application, Design and Control. B. Midcalf, 2004, Pharmaceutical Press.

iv. Isolator design for high volume aseptic units, S Crauste-Manciet, Hospital Pharmacy Europe, 2012,Issue 63, July/ August.

v. New Aseptic Isolator Process for a Cytotoxic Product, D.Thorogood ,PDA Seminar, Basel, Switzerland, 1992.

A biographical note for Doug Thorogood is at the end of Part 1 of this series in Issue 18.