FUTURE ATMP MANUFACTURING PARADIGMS

Dr Dave Seaward
Founder and Engineering Director
E: enquiries@3pinnovation.com

3P innovation LTD
Tournament Fields,
Bosworth Avenue,
Warwick, UK
CV34 6UQ

This final part in this blog series, split into blogs six and seven, by Dr David Seaward, 3P innovation Founder and Projects Director, focuses upon how ATMPs are manufactured, current trends and suggests how the equipment and consumables supporting the sector might evolve. This is based on what the author has observed within a four-decade automation career supporting multiple sectors including — but not exclusively — life science and MedTech.

ASEPTIC PROCESSING AND CLOSED SYSTEMS

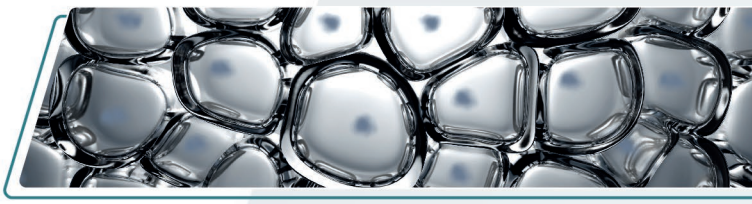
Owing to the fact that ATMPs are injected or infused, there is an added layer of complexity; that is, the need to ensure that the product is not contaminated by any viable or non-viable particulate. Unlike with orally delivered therapeutics, the body really struggles to defend against contaminants delivered into the bloodstream via injected therapeutics: poisoning a patient with a viable particulate into the blood-stream is not an option!

For ATMPs, early production has typically been done by highly skilled/trained laboratory technicians in personal protection equipment (PPE) working in biosafety cabinets (BSCs). This is usually referred to as using aseptic technique, which means using procedures to prevent contamination from pathogens and is similar to those used in operating theatres. Unless you have attempted it yourself, it's difficult to appreciate just how difficult it can be to perform manual operations in BSCs whilst wearing full aseptic PPE!

Despite all the precautions, the human operator remains the biggest risk to patient in terms of accidental contamination of the product. Numerous articles have demonstrated that humans are the main contamination risk in cleanrooms, particularly through the shedding of particles from personal clothing (even undergarments) and skin, which is exacerbated by movement. A typical person sheds around a billion skin cells every day and 10% of them have viable micro-organisms on them. If this wasn't bad enough, we humans need to breathe, which results in micro-organism-loaded liquid droplets being released from our mouths and noses.

Protecting therapies from this risk has led to the use of "functionally closed" and "closed" systems and the implementation of robots. It is likely that, in the near future, regulators will insist that ATMP manufacturers move away from operators in BSCs and insist on closed systems being used.

Functionally closed systems involve products being processed in a closed package (a bag or "tube set," for example) within a Grade C cleanroom. Alternatively, a closed system is an isolator in which the products are processed within a Grade A environment.



WHERE IT ALL BEGAN

Isolator technology can be traced back to handling radioactive materials during WWII. It was Willis Whitfield who invented the modern-day cleanroom in 1962. His innovations led to a 1000-fold reduction in particulates by implementing:

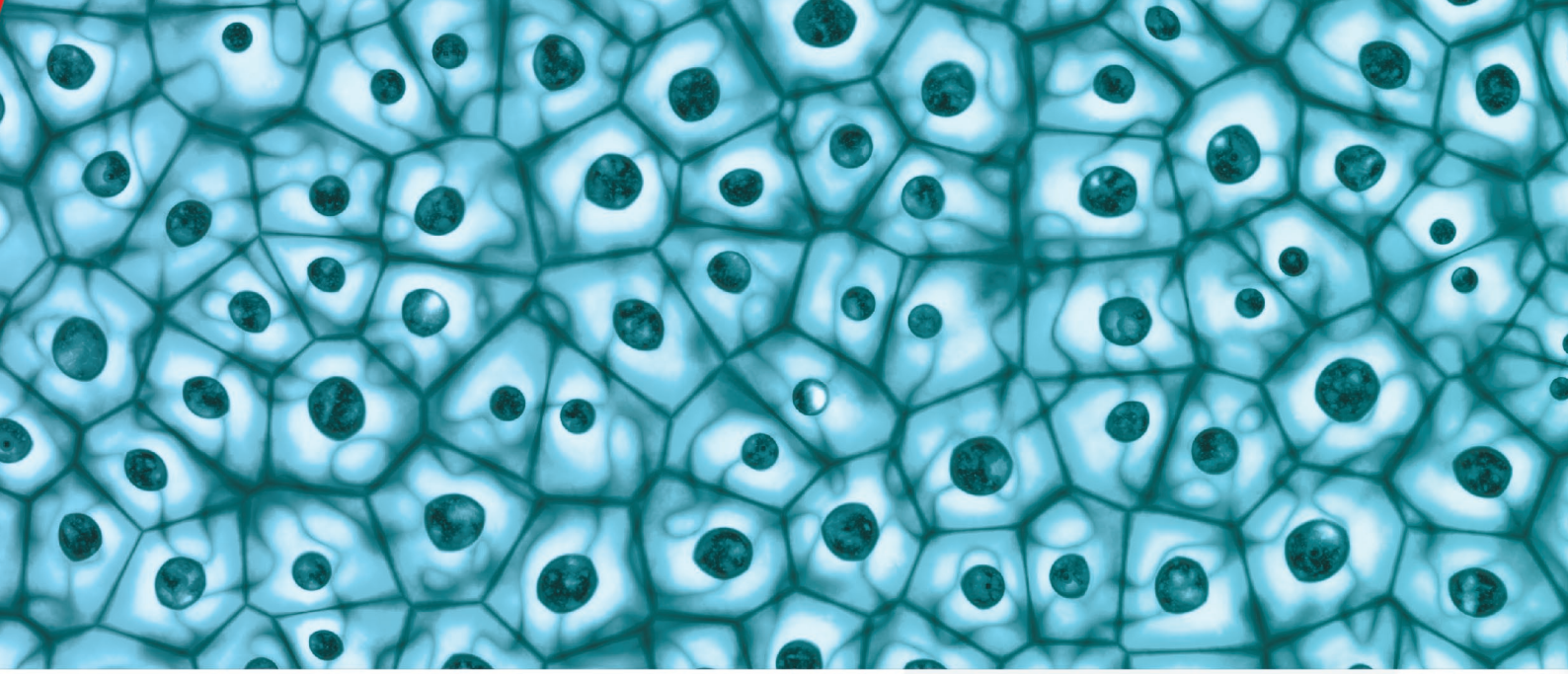
- Highly filtered air to continuously wash away/dilute any impurities in the room
- A linear air speed, which is almost undetectable to operators
- Unidirectional downflow to move particulates in a controlled way away from critical zones.

A 3P innovation aseptic isolator being tested at 3P innovation's UK facility.
(Credit to Azbil Telstar for the isolator)

Isolators were introduced to the pharmaceutical industry in the early 1980s. They drew heavily upon Whitfield's pioneering cleanroom technology, whilst also separating the operator from the process. Isolators with glove ports were utilised to protect operators outside of the isolator against the risk of exposure to a toxic drug ... and to protect sterile products inside the isolator against contamination from operators in the cleanroom. By the end of the 20th century, containment solutions had developed sufficiently to handle the use of complex technologies and equipment, such as robotic arms and powder dispensing systems. Custom automation in this space is one of 3P innovation's core competencies and has led directly to projects in the ATMP space.

Before production can begin, isolators rely on all surfaces being decontaminated — typically with a hydrogen peroxide vapour (some operators also use peracetic acid). Isolators can be hard-wall (constructed from stainless-steel with glass windows and glove ports) or soft-wall (essentially a clear plastic bag welded together that fits over a space frame). A slight positive pressure is maintained in the isolator to ensure that particles from the cleanroom won't enter the isolator and contaminate the product (should a small leak occur). The processing area is fed from above by HEPA-filtered unidirectional air to continuously "wash" the processing area.

Such set-ups may also have systems to enable product to be safely passed in and out of the process area. Sophisticated viable and non-viable monitoring ensures that the production batch has been produced aseptically. A whole industry of isolator manufacturers now exists, with multiple vendors, as well as suppliers of aseptic automation solutions such as 3P innovation. At 3P innovation, we tend to partner with isolator manufacturers for large installations and produce our own small versions.



It should be noted that one of the downsides of standard isolator equipment is that it typically uses hydrogen peroxide vapour as a sterilant (often referred to as VHP or HPV). This absorbs into plastic surfaces and outgasses at minute levels for many hours after sterilisation. Many ATMPs are very sensitive to HPV/VHP, which means that very sensitive monitoring is required prior to production. As a result, it may take a significant amount of time to purge the system following sterilisation. We predict this will lead to the implementation of other sterilant systems. Although currently in their infancy, these may include high-power UVC LEDs and sterilising plasma.

An alternative to an isolator is a functionally closed system. This is a disposable set of interconnected bags and tubes (often called a tubing set) that fits onto a cell processing machine. These tubing sets are supplied pre-sterilised; they can be attached to bags of cells and reagents with sample ports. The equipment has pinch valves, sensors, pumps, heating/cooling and cell processing unit operations, which are automatically co-ordinated via the equipment in response to a recipe.

A number of vendors have developed their own ecosystems of disposable processing containers, bags of reagents and their equipment. The advantage of these systems is that they can operate in a relatively low-grade cleanroom (Grade C) whilst maintaining sterility inside the tube set.

The end-user has a “one stop shop” for equipment and reagents. This can provide significant added value, especially during development. There is, however, a significant risk of becoming “locked-in” to one vendor’s equipment and consumables for commercial manufacture.

The automation aspect is relatively simple in that it sequences peristaltic pumps and pinch valves to move liquids from bags into processing chambers within tube sets, whilst also accurately controlling the temperature and nutrients of the cells.

Another downside is that these machines spend most of their time on one unit operation: cell expansion. The machine acts as an incubator for much of its life and only spends a small amount of time on the other added value and specialist unit operations such as cell separation (usually magnetic), activation and transduction.

As a result, more lab space/equipment is required than necessary from a “cycle-time” analysis. The authors are aware of frustration from end users at being tied into relatively inflexible systems, tube sets and reagents. Some believe an “open source” machine and/or “tube-set” is likely to appear; at the very least, an internationally recognised standard for a common aseptic liquid connector is hoped for.

A closed 90 L bioreactor used in cellulosic ethanol research (http://genomicsgtl.energy.gov/biofuels/)

Different classes of therapies require different unit operations that function at different scales and with different cycle/takt times. The natural consequence of optimisation is the need for divergent solutions for different scenarios. Viral vector-based gene therapies and allogeneic cell therapies lend themselves to larger-scale production than autologous ones.

For example, it is the norm to start process development using small-scale flask-based cultures; these are used to optimise process parameters.
A process can then be scaled into bioreactors for commercial-level production. Such stainless-steel bioreactor vessels can range from tens to low hundreds of litres in capacity.

Batch sizes are likely to increase but, at the moment, they range from a few up to several thousand vials. The filling and closure of vials, so called fill-finish, requires different solutions dependent upon the size of typical batch. Autologous therapies operate at an even lower scale whereby one patient and less than one litre of product represents a batch.

Suppliers of equipment serving these sectors are increasingly offering scale-up/scale-out paths to support their client base. Small benchtop equipment is offered for the discovery phase of a therapy, and larger-scale equipment is then offered for commercial manufacture: suppliers are at pains to demonstrate how processes scale reliability from a small to a larger batch. This would be classed as a scale-up strategy: the batch size increases as the therapy scales-up.

For autologous cell therapies, the trend appears to be towards scaling-out functionally closed systems. This means that there is a very low process risk of scaling as the manufacturer simply buys more of the same piece of equipment. As already mentioned, this relatively low risk strategy also tends to "lock-in" one equipment/consumable manufacturer's ecosystem. This strategy also fits with the "hub and spoke" model for the production of ATMPs and, in particular, autologous therapies.

HUB AND SPOKE

Traditionally, pharmaceutical production has focused on centralising unit operations within large factory complexes. There may be one plant that produces a drug substance, another that converts it into tablets and a final facility for packing. Fundamentally, the focus has been on ever greater efficiencies of scale. Expertise and ever faster/larger equipment is concentrated within "mega" factories. There are many pharmaceutical factories around the planet that generate more than $1 billion of revenue; this model is unlikely to be valid for many ATMPs, however, and autologous cell therapies are an extreme use case.

If the starting material is the patient and unit operations are required following the extraction of a biopsy or bloods, then the natural conclusion is that every hospital or care setting providing a therapy will require specialist equipment. It then begs the question whether it is feasible to do full production within a hospital setting. In the long-term, this may well be the case. At the moment, though, the manufacturing process requires too much involvement from highly skilled operators.

To use the automotive analogy again: a few years ago, driverless cars were deemed to be science fiction and yet we appear to be on the cusp of this becoming a reality. In the future, one might envisage a biopsy being placed into a small, fully automatic low-cost machine, equipped with single-use open-source consumables that an unskilled operator can plug in (think inkjet cartridges). A few days later, the machine "beeps" and a bag of finished cells is ready for infusion back into the patient.

Until these benchtop systems are available, patient biopsies, etc., are likely to be frozen at the "spokes" and then shipped to a central processing "hub." A hub and spoke production model assumes that initial collection, processing and freezing is distributed within the spokes.

The highly skilled thawing/freezing sequence is concentrated in a "hub." Finally, the therapy is distributed back to the spokes to be thawed and administered to the patient. Many in the sector are trying to optimise their therapies around a hub and spoke supply chain model. This needs careful consideration as decisions impact patient safety, therapy efficacy and cost of goods.

3P's Pharma Equipment Discover range of benchtop fill-finish equipment

3P innovation's expertise within pharmaceutical automation has caught the attention of some within this sector, leading to some interesting developments in the ATMP field. In addition, 3P innovation — like other equipment suppliers to the sector — has responded to industry demand for smaller batch sizes and greater equipment flexibility. We have developed both our micro and tub-based robotic fill-finish equipment (see next section).

As a reminder, fill-finish equipment takes a primary drug container (usually a vial), fills it with the therapy (usually a liquid but sometimes a powder) and closes it to provide aseptic assurance (usually with a rubber stopper and an aluminium crimp).

The core unit operations of these systems are based on pre-existing designs that were generated on the back of large custom aseptic pieces of automation. By retaining tried and tested filling closing/stoppering and crimping technology throughout the range, scaling risks are minimised. 3P innovation therefore offers a scale-up strategy from discovery to commercial-scale for ATMP fill-finish.

ROBOTS, "GLOVELESS ISOLATORS" AND TUBS

Industrial robotics are seeing a boom across many industrial sectors. This is being driven by a need for improved product quality, greater assembly precision, reduced labour costs and increased automation flexibility (for mass customisation, for example). In previous decades, the cost of robots often precluded implementation; however, ever lower equipment prices and increasing labour costs are now garnering rapid paybacks.

The unit operations associated with many aspects of ATMP production remain very manual and, as such, manufacturing facilities are having to adapt to ever smaller batch sizes. 3P innovation is not alone in developing flexible automation systems that are optimised for small batches. One trend that 3P innovation has observed relates to more compact and flexible machines filled with small pieces of equipment connected via robotics. Some vendors are offering low volume fill-finish with no glove ports.

Although this may be feasible for simple unit operations involved in handling and filling vials, it remains an expensive choice if any interventions are required. Potentially, a whole batch of very costly therapy could be wasted! Thus far, 3P innovation's clients have retained the gloved option "just in case." Gloves offer a relatively low-cost insurance policy and, like any insurance, it's better if it's never needed. As processes become more robust and interventions become improbable, gloveless systems will inevitably become more commonplace.

In traditional high-volume fill-finish facilities (think vaccines), it makes sense to source vials in bulk and depyrogenate just prior to the fill-finish step. ATMPs are, however, high value and low volume. This is driving the trend towards pre-sterilised tubs containing nests of primary drug containers (vials, prefilled syringes [PFS] and cartridges, etc., in tubs that are compliant with ISO11040-7:2015en).

This has led to smaller, slower and more flexible fill-finish production equipment. They do a rapid sanitisation of the outside of the tubs prior to removal of the outer plastic bags. Ahead of fill-finish, a further barrier in the form of Tyvek™ lids are removed. Robots are the natural automation solution to de-nesting (and re-nesting) tubs of primary drug containers.

Simple changes to the robot end effector enable the same equipment to remove the Tyvek™ lids, process vials, cartridges, PFS and novel primary drug containers when packaged in ISO-standard tubs. To minimise development, many vendors of aseptic automation solutions have elected to use “standard” robots — albeit to cleanroom/sterilisable standards. Robots developed specifically for the demanding requirements of aseptic processing are now readily available; these have features such as the ability to seal against HPV/VHP sterilants, accommodate non-shedding coatings (or stainless skins) and, although it might seem trivial, also have bottom entry electrical connections (side entry is the norm for industrial robots). Modern robots can also come with dual redundant systems, which are inherently safe because they can interact securely with operators in a collaborative way — so called “cobots.”

3P innovation's robotic tub-based fill-finish solutions using six-axis aseptic cobots

Like many vendors of aseptic automation, 3P innovation has a range of “standard” aseptic modules that can be employed as required. Hence, we have a range of modules to de-lid and manipulate tubs, and de-nest/re-nest devices into tubs. We have a range of liquid dispensing pumps and lift/rotate modules to enable aseptic liquid filling. There are stopper feed bowls and stoppering modules (including vacuum stoppering and nitrogen/gas purge). Finally, we have low particulate generating crimping modules.

These subsystems can then be “glued together” by robotic solutions and placed into isolators. As already mentioned in the previous section, these same unit operations have been packed into 3P’s Pharma Equipment Discovery range benchtop units, which may be operated in a BSC/isolator.

3P innovation currently has two robotic offerings; we’ve developed our own compact aseptic robot, which is capable of compact X-Y movements and, for more complex movement, we employ Stäubli’s TX2 range of aseptic six-axis collaborative cobots. The cobot feature facilitates safe integration with manual operations and enables the guard line to be within reach of the robot (to minimise the size of any isolator). All of 3P innovation’s aseptic robots are sealed against hydrogen peroxide sanitisation and, crucially for aseptic processing, do not shed particulates.

Being like a human arm, six-axis robots are very flexible … but are often larger than necessary. This can lead to excessively sized isolators and cleanrooms. More recently, vendors have begun to introduce their own compact robots. By way of example, to overcome space constraints in isolators, 3P innovation introduced their “Crabot” two-axis robot. It uses two rotary axes, which is ideal for aseptic applications, to create the X-Y motions required to manipulate a tub of components.

Notwithstanding the desire for more robust processes, robots enable a significant reduction in particulate generation. Much of the ATMP sector currently relies on skilled artisans to do the necessary unit operations in a BSC. As per the analogy in the first of this series of blogs, the sector currently resembles Rolls-Royce hand producing small volumes of high-cost products. These costs will be reduced by automation. It is inevitable that automation will play an increasingly important role across all areas of ATMP production. Robots are just one part of the automation “mix.” However, with time, if it can be automated it will be!

The ideas and topics discussed in this blog will continue in the seventh and final part of this blog series where the author will look into the increase of computing power and the impact of AI as well as the use of “primary drug containers” and the idea of “Lost cells”.

A 3P tub-handling “Crabot,” Note the X-Y output generated through rotary joints leading to a compact aseptic automation solution