Future ATMP Manufacturing Paradigms Part II

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

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

Following on from part six of the blog series, we continue to take a look at the future of ATMPs' manufacturing paradigm.

INCREASING COMPUTING POWER, THE CLOUD, INDUSTRY 4.0 AND AI

Artificial Intelligence (AI) is another form of automation. No forward-looking blog can ignore the likely impact of AI on a sector – and ATMPs are no exception. Despite being a stringently regulated industry, ATMP developers are very much active in the so-called Industry 4.0 initiatives. The complex nature of the datasets generated by ATMPs naturally lend themselves to advanced multivariate analysis and algorithmic procedures to create powerful insights.

Microbioreactors are popular because of their small footprint. They are becoming increasingly sophisticated with the ability to control sparging, head gasses, feeding and temperature control, as well as incorporate metabolite measurements. Rather than progress through a known sequence of set-points against time, modern systems can adjust their set-points in real-time. AI-enabled controllers have the ability to learn and dynamically adapt, which is particularly important for autologous therapies whereby the incoming raw material varies considerably from patient to patient.

An AI system is possibly the only practical means of optimising such a complex dataset. A traditional controller would process every batch of cells in the same way. Unfortunately, especially for autologous therapies, this means that not all patients would receive an optimised therapy. AI offers the ability to adjust to the variability of the incoming raw material. And, although this all sounds very complicated, it's worth remembering that modern dishwashers include simple turbidity sensing to check how dirty the recycled cleaning water is becoming. In response to this simple sensor, the amount of washing (and energy) is directly related to the amount of dirt! Old machines simply ran through a fixed sequence and didn't respond to the load. The term "AI" might make this sound more complex than it really is. Using CQAs and CPPs to better understand a process is key to unlocking this puzzle.

From this simple analogy, it's worth noting that humans have approximately 2000 miRNAs, 20,000 proteins, 30,000 mRNAs and 100,000 metabolites. Yet, it's becoming feasible to measure all these. It then becomes possible to monitor patient outcomes using AI and then learn how best to treat a patient. The Star Trek tricorder, which scans a patient and tells the physician what to do, remains science fiction … but only just!

At the moment, certain therapies are known to work in some patient groups and not in others: AI offers the ability to join the dots of cause and effect. This ensures appropriate treatment and better patient outcomes, which becomes even more important when innovative payment models are considered — such that the producer is not paid per treatment but on therapeutic benefit per patient per year. Then, knowing the right patients to treat becomes significantly more important.

With all this data, only sophisticated AI can tease knowledge from these large datasets, thereby making it increasingly important and valuable. There is significant interest in terms of accessing the UK's NHS network as it represents one of the more "joined-up" healthcare systems. This ability to track anonymised patient data will drive the ATMP sector forward. This data is likely to reside in the cloud in some form of secure quality management and information system. And although AI can deal with unstructured data, it will become increasingly important to structure the information — all the while acknowledging that hybrid data (semi-structured) is likely to appear from disparate sources (analytical instruments/lab reports, etc.).

Labelling data to ease the application of advanced tools will also be paramount. AI will help humanity to learn which factors will most likely influence a positive patient outcome. This, in turn, will lead to advanced diagnostics to target specific patients who will respond to a treatment. From an automation perspective, we will learn which parameters need to be more accurately controlled: this leading to better sensors and better means of control in specific areas (such as the implementation of precision force and measurement in tablet presses to control tablet weight).

Another area in which modern computing has a significant role to play is augmented/virtual reality. To overcome staff shortages and reduce the risk of operator error, manual lab processes are starting to use "digital twins." The UK's very own Cell and Gene Therapy Catapult has partnered with FourPlus to offer immersive ATMP laboratory training using digital twins. It has been shown to speed up the education of laboratory staff, leading to significantly lower training costs.

Beyond virtual reality, augmented reality (AR) is also being trialled. With AR, operators can be monitored and assisted with a digital overlay on top of reality. A trainer can monitor and guide an operator remotely; plus, any given process can also be monitored automatically, with data from the operator and equipment being loaded to the cloud for analysis via AI, as discussed above. There is a new world of opportunity that is opening up for developers of ATMPs as a direct result of ever-increasing computing power, digital twins and AI algorithms. This can only speed up the development of novel ATMP therapies.

PRIMARY DRUG CONTAINERS

The receptacle for an injected drug substance is usually referred to as the primary drug container (PDC). The borosilicate glass vial remains the go-to PDC for many injectable therapies. Owing to the complexity of administration involved in decanting from a vial, there has been a preferential trend towards prefilled syringes, prefilled cartridges and autoinjectors. The majority of syringes and prefilled syringes in use today, comprise borosilicate glass with butyl rubber stoppers and aluminium crimp caps. Injected therapies may launch in vials but, quite often, the brand is "extended" for convenience with the introduction of pre-filled syringes or autoinjectors. With one or two exceptions (such as ocular), ATMP therapies rely on the infusion of millions of cells. The need for infusion has meant that there are two main types of PDCs used for ATMPs.

Cells are dispensed into either large vials or infusion bags (usually referred to as cryobags for reasons that will now become obvious). After filling with cells, the PDC is usually stored and cryopreserved in liquid nitrogen (LN2) at temperatures of approximately –180 °C. They are then shipped to points-of-care by specialist couriers using dry vapour (Dewar) shippers. They can be thawed and infused at the bedside: remember most hospital pharmacy services do not have access to LN2 freezers. Recently, and partly driven by issues associated with COVID, dry ice (–80 °C) has also been used to preserve ATMPs. It should be noted, though, that thermal shock in the form of too-rapid thawing can destroy a valuable gene therapy, notwithstanding presenting a risk to patients. As such, the pharma cold chain industry is rapidly evolving to transport frozen ATMPs safely.

Anyone who has ever dropped a glass drinking vessel on a hard floor will attest to how brittle glass is at room temperature. Imagine how brittle it is when frozen? This has meant that plastic vials (typically made cyclic olefin copolymer or COC) are becoming the go-to material for ATMPs. Glass containers simply can't handle the challenges of cryogenic storage, nor can they maintain seal integrity at these temperatures. The butyl of the rubber stopper and the glass of the vial expand/contract differentially, meaning that container integrity is at risk. Issues such as breaking and cracking when the vials are handled or thawed to room temperature can be wasteful. COC PDCs are also tolerant to autoclaving. As we have already discussed, one vial of therapy may have a cost significantly higher than the value of the PDC, such that glass PDCs are becoming increasingly rare around ATMPs.

At the moment, suppliers such as West Pharma, SCHOTT and Mitsubishi have chosen to mould vials and cartridges to mimic the shape of equivalent glassware. This eliminates any equipment modification when moving from glass to plastic. The shape of glassware is limited by the nature of glass and how it's converted into PDCs. COC can, however, be injection moulded and, unlike glass, can include fine detail. This opens up the tantalising possibility to form new and novel PDCs with features that provide significant benefits.

“LOST” CELLS

Our earlier blogs explained how costly ATMP therapies can be. Any waste comes with a high price tag and, given the number of pipes and surfaces that processing fluids come into contact with during production, a significant amount of viable and costly therapy is inevitably left behind. It is interesting to note the USP recommendation regarding excess amounts for liquid injections using vials and syringes (Table I). It can be seen that the smaller the fill volume, the higher the recommended overfill. It is initially staggering to see this varies from 3–24% of the fill volume.

Imagine leaving 24% of a very costly therapy behind in a tubing set! For one specific therapy, 3P engineers did a Gage R&R study using weight measurements to identify where product was being left behind. Typically, each unit operation suffered a 0.25–2.00% loss of product. Before the exercise, the client didn’t know where the biggest areas of loss were. With hindsight, some may have been obvious ... but others less so. Armed with this data it was possible to suggest improvements. A Monte Carlo simulation was generated by 3P’s engineers based on the experimental results. Suggested improvements could be tested in simulation to justify implementation. As one might expect, some improvements were trivial to implement whereas others required significant investment to change tooling, etc., or involved a change in process (potentially requiring revalidation). The exercise enabled a reduction in losses for relatively minimal expenditure.

Table I:
>USP recommended overfills to compensate for liquid left behind

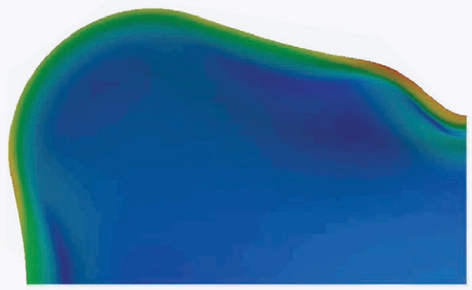
LABELLED SIZE (ml)	MOBILE LIQUIDS (ml)	%	VISCOUS LIQUIDS (ml)	%
0.5	0.1	20.0%	0.12	24.0%
1	0.1	10.0%	0.15	15.0%
2	0.15	7.5%	0.25	12.5%
5	0.3	6.0%	0.5	10.0%
10	0.5	5.0%	0.7	7.0%
20	0.6	3.0%	0.9	4.5%
30	0.8	2.7%	1.2	4.0%
50	1	2.0%	1.5	3.0%

It is within the public domain that 3P has worked on two such innovations. Oval Medical Technologies (part of the SMC Group) has developed a compact and unique autoinjector; at its core is a proprietary COC PDC. Many of the reported benefits are delivered by features not available on standard fill-finish equipment, which is where 3P comes in!

Similarly, SteadyMed Therapeutics came to 3P for specialist assembly and fill-finish automation for their patch pump PDC (formed from a COC moulding welded to a COC flexible laminate). We expect to see innovation in the functionally closed tube sets, as well as PDCs, being driven by the ability to mould and weld COC in response to therapy production and delivery needs.

The ability to add features via injection moulding to the primary drug container enables the medical device designer to get really creative: expect some really innovative COC-based PDCs for ATMPs very soon!

COC is not without its challenges. It also becomes increasingly brittle at low temperatures. Indeed, 3P was engaged several years ago to identify the root cause of cryobag thawing failures. A client was using the same bag at several manufacturing hubs; yet, on thawing, some hubs suffered from a leakage rate of >5%. Other hubs were below 1%. All the leaking bags were scrapped at significant cost. The root cause was identified as the stresses induced around the creasing that naturally occurs during filling. The stress led to leakage at cryogenic temperatures as the polymer bags could not withstand these temperatures. This effect was simulated in silico using a finite element package (see below). As with many initially seemingly unsolvable problems, the final solution came down to understanding the root cause of the issue. The solution, in this case, involved some relatively trivial procedures to manage bag inflation.



>A finite element simulation of a cryobag showing the regions of high stress caused by creasing

CONCLUSION & FINAL THOUGHTS

As we draw this series of blogs to a close, what have we covered and what have we learned? The first blog discussed the challenge around cost of goods for ATMPs and also the shortage of appropriate skills to develop and produce them. The second and third blogs provided some historical context about the various technologies behind ATMPs and the fourth blog explained 3P's product agnostic methodology for the development of automation for MedTech devices, which is as applicable to ATMPs as it is for injector pens or inhalation devices.

The fifth instalment delved back more than 100 years into the history of the pharmaceutical sector to look at what lessons might be learned for ATMP production. For anyone working in ATMPs today, it's comforting to know that originators in other life science technologies remain in business a century later.

Even though original unit operations remain in place, improvements are made to enhance process robustness, speed of production and cost of goods. Sectors fragment as new therapies arrive and an ecosystem of vendors (equipment, consumables, excipients, etc.) evolves to support Big Pharma manufactures. And whereas many batch processes remain, others have converted to continuous processing for cost-efficiencies and optimisation.

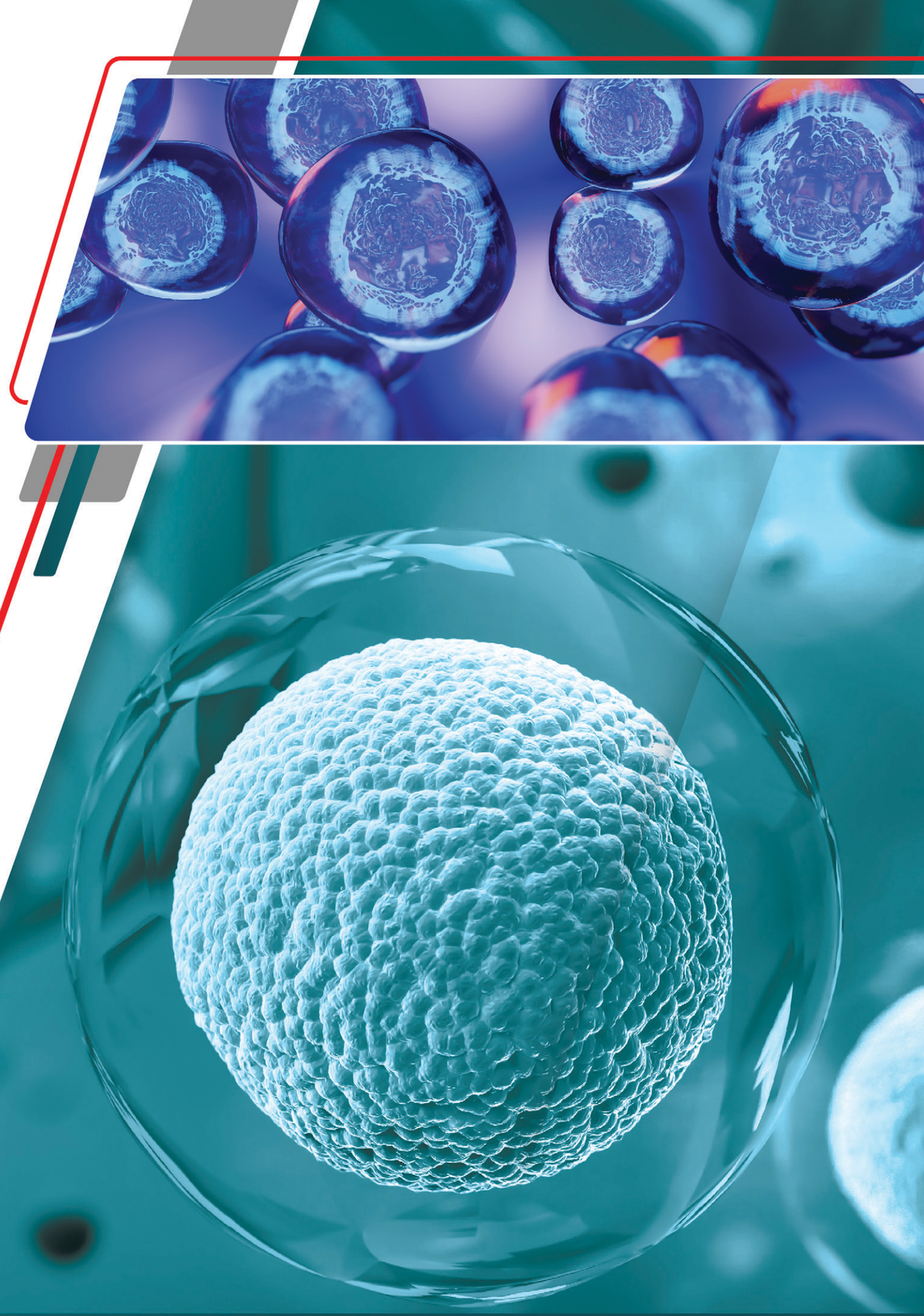
It's likely that, with time, the core ATMP processes in place today will remain. No doubt, they'll be refined to increase throughput and quality, so expect to see larger-volume processes being converted from batch to continuous. Equipment complexity, especially in terms of sensing and control, will certainly increase. It was noted that takt and cycle times are particularly important for ATMPs, wherein cycle times can vary dramatically for different unit operations. As yet, there is no clear solution to this conundrum. We suspect that each therapy area will develop its own preferred automation equipment and infrastructure because, for example, the needs of an autologous cell therapy are simply too different to a viral vector-based gene one.

The final sixth and seventh parts (for now!) observed that ATMPs are likely to stay as injectable/infused therapies that are contingent on aseptic processes. It is likely that the sector will fragment into those therapies that suit functionally closed systems versus those that utilise closed isolators. Both systems will see ever-increasing complexity in terms of sensing and feedback loops.

The consumable "bag set" of functionally closed systems will change and may be unrecognisable in the future. Primary drug containers made of COC plastics will further enhance the process by minimising cell loss and we hope to see open-source standardised containers or, at the very least, aseptic liquid connections. For closed systems, the time of robots is near, which will usher in more robust, reliable and gloveless processes. Plus, to avoid the long degassing times associated with hydrogen peroxide sensitivity, alternative sterilants such as plasma and UVC will be employed.

All equipment vendors will need to offer scalability from benchtop to commercial production. The ATMP sector is likely to adopt AI, the cloud and Industry 4.0 technologies earlier than would normally be expected for the highly regulated pharmaceutical industry. Tracking patient-specific therapies digitally through the supply chain will become an increasingly important supporting technology. And, whereas larger-volume therapies will follow the classic route of centralised factories, the localised and patient-specific nature of other treatments will drive a decentralised hub and spoke model with different forms of automation.

It's always dangerous to predict the future. Some of what we speculate is already happening and some remains conjecture. Our thoughts are founded in what has been personally observed within other life sciences sectors during the last century. We hope you find our insights into this exciting therapy area of interest. In a hundred years, will we be able to look back and see who ended up being the Ford (or more likely the Fords) of the ATMP sector? We are hoping and planning for 3P to be part of this journey.



+44 (0) 1926 408 933 enquiries@3pinnovation.com www.3pinnovation.com

BIBLIOGRAPHY

1. US Department of Health and Human Services Food and Drug Administration Center for Biologics Evaluation and Research, Guidance for Industry. PAT— A Framework for Innovative Pharmaceutical Development, Manufacturing and Quality Assurance (2004): www.fda.gov/media/71012/download.

2. M. Frické, "The Knowledge Pyramid: A Critique of the DIKW Hierarchy," Journal of Information Science 35(2), 131–142 (2009).

3. https://database.ich.org/sites/default/files/Q8_R2_Guideline.pdf

4. www.ema.europa.eu/en/documents/scientific-guideline/international-conference-harmonisation-technical-requirements-registration-pharmaceuticals-human-use_en-3.pdf

5. www.ema.europa.eu/en/documents/scientific-guideline/international-conference-harmonisation-technical-requirements-registration-pharmaceuticals-human_en.pdf

6. R.S. Kenett, "The Role of Statistics in Quality by Design Initiatives," Six Sigma Forum Magazine (November 2009).

7. P. Belliveau, A. Griffin and S. Somermeyer, Eds, The PDMA ToolBook 1 for New Product Development (John Wiley & Sons, Chichester, UK, 2002).

REFERENCES

- https://biotechprimer.com.
- www.gov.uk/government/consultations/point-of-care-consultation/consultation-on-point-of-care-manufacturing.
- www.biopharminternational.com/view/impact-atmp-manufacturing-process-equipment-and-facility-design.
- www.cellandgene.com/doc/how-cell-and-gene-therapy-is-transforming-healthcare-0001.
- https://spectrum.ieee.org/engineering-a-medical-revolution.
- https://atmpmanufacture.org/wp-content/uploads/2016/10/Jef-Pinxteren.pdf.