

Putting your ATMP Process on the Map: Strategies for Scaling Out Facilities to Meet Commercial Development Realities

Cell, gene and tissue therapies are transforming medicine, showing meaningful efficacy in treating – or even curing – diseases once thought intractable. Known as Advanced Therapy Medicinal Products (ATMPs) these modalities exhibit the potential to cure disease by addressing its root cause rather than treating it symptomatically.

Recent approvals of ATMP breakthroughs such as Kymriah, Tecartus and Yescarta exemplify the exceptional advancements in this space. According to Grand View Research the global market ATMP's is projected to expand at a compound annual growth rate (CAGR) of 13.2%, with market expected to reach \$21.2 billion by 2028.¹

These approvals have spurred a flow of investment which is expected to help accelerate the pace of development and patient access. Grand View Research notes innovators are now adopting various operation models to accelerate the autologous ATMP product manufacturing process.

A Sharp Shift to an Age-old Paradigm

Autologous ATMP therapies require human cell harvesting and therefore these processes begin with the patient. The processing ideally takes place in cleanroom environments located close to medical centres and centralised healthcare systems. A patient's proximity to the process is essential because it can significantly improve product quality and patient experience.

Harvesting cells, treating them and reintroducing them to the patient is prompting the industry to rethink how to manage the patient experience as part of the ATMP supply chain. The patient's direct involvement as well as (for now) the manual processing involved in autologous and allogeneic production methods insert operational risk into manufacturing that will affect product scalability.

Modular Technologies Delivering What ATMP Innovators Need

Cleanrooms were traditionally fabricated on site using stick-built wall-board construction

methods. For much of pharmaceutical plant history, the fact that this method was cumbersome to engineer and slow and expensive to construct was not an issue – as long as it functioned, was validatable and compliant. The capital expense associated with cleanrooms was seen as financially tolerable relative to the economies of scale associated with centralised large-scale pharmaceutical manufacturing facilities.

The demand for affordable, more effective drugs as well as the need to reduce the overall costs of drug development and manufacturing have all served to turn traditional pharma facility operational models on their head. Emerging drug development business models also influenced the industry to improve the commercial implementation of complex cleanroom spaces and help make construction as cost efficient as possible. These drivers led to increasing development of modular, pre-fabricated solutions that wrap around the space to contain it as well as ease the complexities, time and cost of erecting facilities.

Modular Systems Ideal for Autologous Processing Siting Flexibility

Over the past two decades the concept of modularity in cleanroom engineering and construction has matured significantly – especially to meet the evolving, dispersed manufacturing demands of delivering ATMP treatments to patients. Although cleanroom modules encompassing entire three dimensional spaces have been implemented, the ideal modularity solution in this instance refers to a component-based wraparound facility that leverages modular architectural technology along with high-performance environmental systems, all of which are prefabricated in a controlled factory environment. These modular systems are flat-pack shipped and ready to assemble within any host building's unique footprint, all under clean conditions. This approach is more flexible and cost effective than 3-D solutions and is higher quality with quicker validation timelines than traditional stick-built facilities. This middle-ground modular solution is proving to be the most effective way to implement repeatable cleanroom facilities across a multi-site ATMP network.

Drug delivery strategy often dictates these sites must be located near population-centers and possibly even within dense urban environments. In these locations, what is considered suitable and available commercial building stock can vary wildly. For these reasons and more, the wraparound cleanroom solutions manufactured by today's suppliers, for example, are purposely engineered to accommodate virtually any viable floor plan both horizontally and vertically.

Site location is a critical element to program success but so is selecting the right host building. Fortunately, industry experience has revealed a common set of optimal building “denominators” that can help host building selection and optimise modular cleanroom installation build-outs. (See sidebar Selecting the Best Host Building for Program Success)

Since the first cell therapy was developed and subsequently approved nearly 15 years ago, ATMP drug developers along with their modular cleanroom solutions partners have learned a thing or two about building out production capacity to help launch these programs successfully in support of critical development timelines and product approval milestones:

Derive a Production Plan

Do you have a Demand/Supply Plan?

The forecast should be a top-down assessment, starting with the finished commercial goods demand. Integrating risk management and contingency factors are also prudent in maintaining supply continuity, which includes ongoing pipeline clinical studies.

As a project's development crosses a threshold from early phase success to later clinical trial, so does the need to obtain a clear projection of the demand for the treatment as well as a clear validatable process (including containment) for the drug product. Commercial production requirements represent a higher standard of current Good Manufacturing Process (relative to localised protection, product traceability, cross contamination controls, etc.). Considering the high unit cost of a purpose-built, regulated facility, it is prudent



Shown here is a cleanroom facility responsible for a CAR-T treatment that was located on the 9th floor of a 16-story building on an urban hospital campus. Presenting challenging project logistics, the existing space compressed the cleanroom facility both horizontally and vertically due to extremely low floor-to-floor heights. Hugging the all-glass exterior of the skyscraper's custom envelope, the cleanroom facility's modular technology allowed it to wrap around the process and protect patient material while maintaining the views of the surrounding cityscape.

to configure ATMP manufacturing operations to support the needs of this particular segment of drug development.

Whether a company makes or contracts the manufacturing supply chain, this will likely be the largest investment/commitment in the company's history. A forecast allows a company to communicate on multiple levels with contractors, suppliers, management, and executive teams in rationalising resources needs, focusing on goal specifics, and negotiating high value contracts.

Confirm Make vs. Buy

Is your post approval supply chain going to be internal or externally provided?

A second highly consequential success factor is a company's decision and plan to manufacture internally (Make) or externally using outsource manufacturers (Buy). Outsourced "contract" manufacturing has historically enabled the entry of many new drugs into the market. But as the industry continues to develop ATMP therapeutics, the complexity of the science and its manufacturing processes have also increased—and that includes the value of intellectual property.

With the inherent evolution of these sensitive manufacturing processes, a developer and its investors may feel the best business strategy is to retain the deeper knowledge and therefore financial return from developing and building out its own process infrastructure. A build-out strategy leveraging modular cleanroom technologies with turn-key solution partners may offer distinct economies and preclude sharing intellectual property with external contract manufacturing organisation partners. On the other hand, a CMO offering a similar operational and technical template might make the best organisation to partner with if it supports successfully achieving drug program goals and timelines.

Therefore, within the context of ATMP development the Make vs Buy decision becomes a serious consideration and should be evaluated early, certainly prior to Phase III. A conservative plan might include a "bridging" strategy where a company might launch a new product from a CMO and then plan to transfer manufacturing early to a self-owned facility upon assurance of FDA product approval (and a revenue stream).

Define/Document the Manufacturing Process

Have you defined your manufacturing process?

The single greatest influencing factor on the design and cost of an ATMP facility is the process's design. It must be housed in a fit for purpose facility. Because the process is the product, designing the physical facility requires first defining the process's critical quality attributes (CQAs) then determining its flow and floor plan relative to the host facility structure.

A process flow diagram (PFD) can facilitate fit-for-purpose objectives. When applied and qualified properly, aseptic single use technologies can effectively "close" processes. The result will simplify facility design, reduce square footage need, diminish regulatory scrutiny, increase process change flexibility, and enable product transferability or portability.

Many cell and gene therapies have inherently small batch operations, which may further leverage these opportunities. A well-documented PFD enables designers to meet clinical, commercial and development



product needs based on a necessary capital budget estimate.

Build Cross-functional Teams Is a team identified and sanctioned?

No external consultants will ever know the technical, operational, or strategic objectives better than a company's internal subject matter experts. Therefore, without the benefit of a cross-functional team, there is greater risk to project success. The team should minimally include members from Manufacturing, Development, QA/QC, Regulatory, and Sales & Marketing. Where experience gaps may reside, engaging consultants is a common strategy to supplement a team in gaining broad experience, completing high level tasks, and objectively challenging rooted norms.

Actualise Facility Build Out Strategy with a Modular Approach

Considering that it takes hundreds of experienced staff (and tens of thousands of hours) to commercialise an ATMP drug product, the sooner resources are focused on a cohesive company build-out plan, the sooner commercial success can be achieved. As a pioneer of turnkey cleanroom solutions, AES understands that modular approaches to cleanroom deployment can deliver significant capital expense control as well ongoing operational benefits.

Modular cleanroom solutions support key ATMP development goals, timelines and objectives including regulatory agency approval milestones and process validation. Over the past 15 years, modular cleanroom

Selecting the Best Host Building for Program Success

The intent is to use this facility as a manufacturing asset, to include GMP cleanroom space along with support laboratories, warehouse, and office space. The following are key areas of consideration when evaluating the suitability of a host building to accommodate a GMP facility.

- **Building Use Group** (inherent construction of host building to accommodate manufacturing, especially if multi-tenant facility)
- **Building Cross Section** (sufficient vertical height, not only for storage but also for cleanroom HVAC infrastructure)
- **Building Access** (for both personnel and materials deliveries)
- **Floor Loading** (suitable slab to accommodate weight of manufacturing and storage)
- **Utilities** (sufficient power, water, sewer, gas, data, fire protection)

solutions have become a key enabler in the safe and effective delivery of ATMP therapies, and with each breakthrough continuing to deliver the capabilities required to achieve commercial success and better patient outcomes.

REFERENCES

1. <https://www.grandviewresearch.com/industry-analysis/advanced-therapy-medicinal-products-market#:~:text=products%20market%20growth%3F-b,USD%2021.2%20billion%20by%202028.>



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Grant Merrill is the CEO of AES Clean Technology. He has been involved with cleanroom design and construction for more than two decades. Grant earned his BS in Mechanical Engineering from Cornell University, and built a successful career in the industrial HVAC engineering business before joining the AES team in 2001. At AES he enjoys leading multi-disciplinary teams to deliver complex cleanroom facilities to clients throughout the life science industry.