aes Clean Technology

ADVANCED THERAPY MEDICINAL PRODUCT CLEANROOM FACILITIES: A ROADMAP FOR SUCCESS

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INTRODUCTION

We are in the midst of a next-generation scientific revolution in personalized therapeutic medicine. However, the design of manufacturing infrastructure continues to follow an outdated playbook. Current advances in cell, gene and tissue therapies require a rethinking of how—and where—cleanroom manufacturing facilities could be built, enabling more options for sponsor process control.

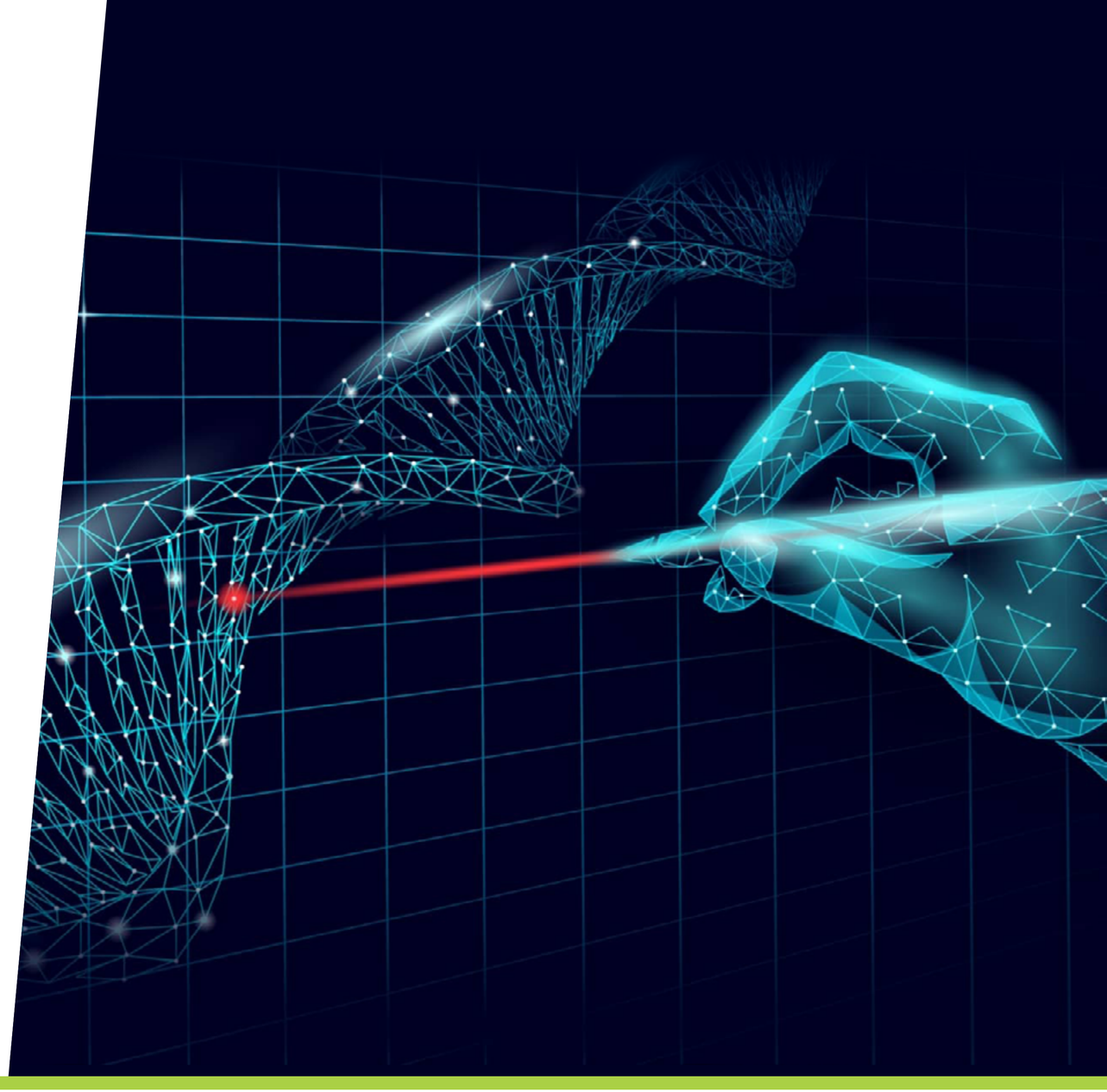
Cell, gene and tissue therapies have transformed medicine, showing meaningful efficacy in treating—or even curing—diseases once thought intractable. Also known as Advanced Therapy Medicinal Products (ATMP), these new treatments represent a significant medical advancement based on the knowledge gained from the human genome. ATMP is only now emerging from the "early days" of this field, and the scalability of these techniques continue to offer challenges to the design of manufacturing facilities.

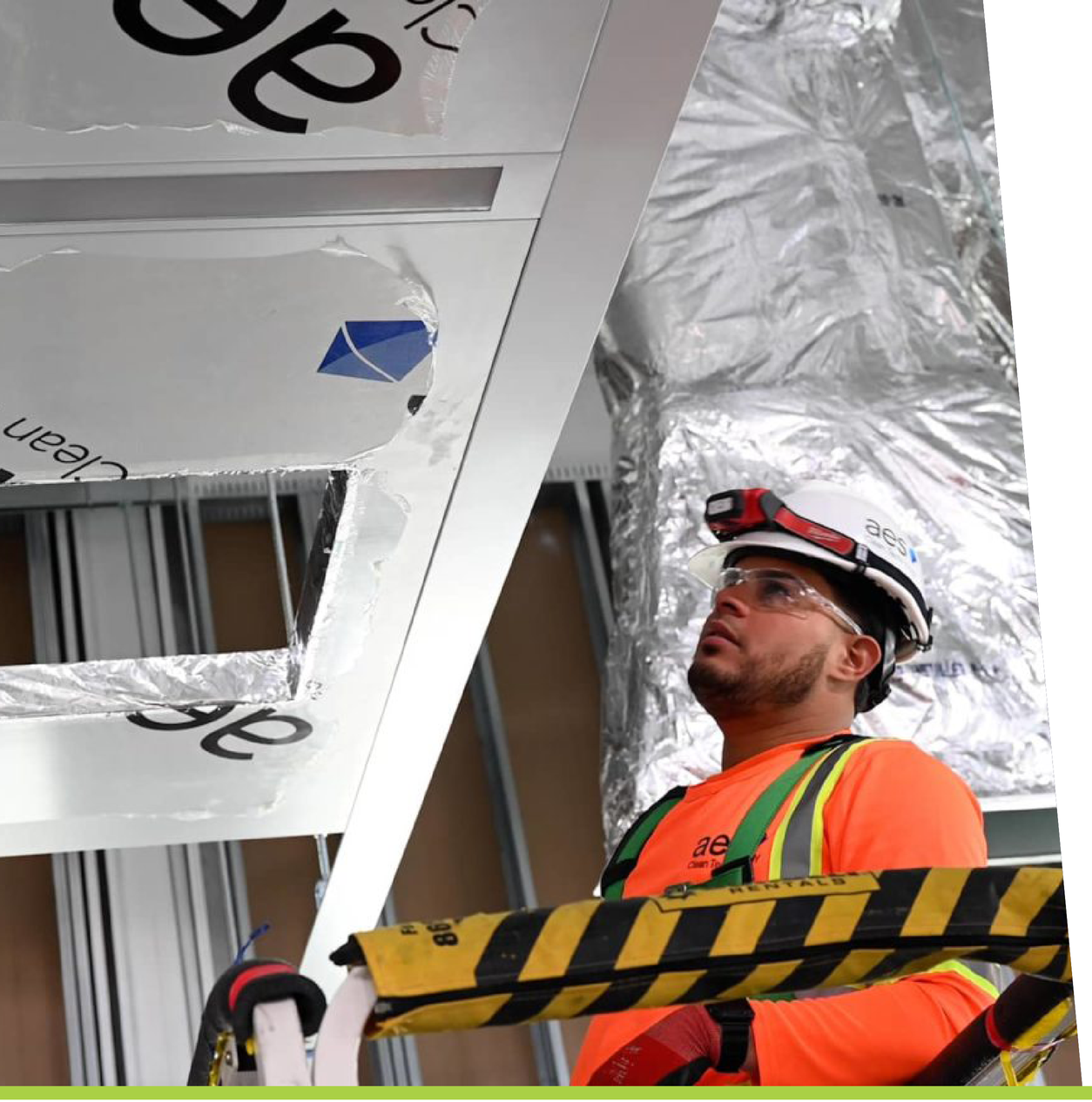
In particular, manufacturers are pioneering new pathways to create cleanroom facilities that combine both advanced science and manual dependent processes. In this article, we take a look at lessons learned from more than a decade's experience in building ATMP cleanrooms in order to help manufacturers chart their roadmap for success.

Autologous therapy requires human cell harvesting and therefore these processes start and begin with the patient. This ideally would take place in a cleanroom environment logistically closer to medical centers, which would significantly improve patient treatment as well as product quality. The logistic challenges and manual processing involved in autologous and allogeneic production methodologies insert operational risk into manufacturing that will affect product scalability.

The life-changing reality of cell, gene and tissue therapies are also driving changes in both the regulation and design of the cleanroom facilities that are essential to the production process. The wide acceptance of single use technologies and relatively small production batch needs (i.e. smaller facility footprint) have presented a significant opportunity for start-up companies to take control of their destiny earlier in a product's lifecycle by considering the option of early production facility ownership along with process and supply chain direct control. Also, greater protection of intellectual process knowledge is an added benefit.

Over the last 15 years, AES Clean Technology has adapted to meet the evolving needs of ATMPs by designing and installing numerous purpose-built cleanrooms for emerging cell, gene and tissue therapies, a portfolio that also includes multiple COVID-19 Warp Speed projects. This experience has helped AES develop cleanroom design build templates that harness the knowledge of best practices for this nascent field. We have learned there is a commonality among cleanroom project success factors that are in compliance with regulatory standards. This article is intended to share these experiences on what factors are central to successful entry into commercialization of new therapeutic production capital projects.





CLEANROOM DESIGN FOR SCALE

For cell, gene, and tissue therapies, there is a distinct relationship between success and scalability. Successful therapies generate demand that can only be sustained through the scalability from the laboratory, pilot, and eventual commercial manufacturing cGMP space.

There are three prominent methods of building cleanrooms, but only modular cleanroom installation allows for both the rapid flexibility and scalability that modern autologous and allogeneic facilities require.

The traditional stick-built, drywall-based architectural cleanroom construction has perceived short term advantages in terms of both material availability and the lower cost of unskilled labor but those come at cost when increased capacity is needed. Stick-built cleanroom facilities use outdated organic materials of construction, are high maintenance, and lack adaptability to meet even minimum standards for cleanliness and low particulate count often inducing significant operational disruption at a time when commercial supply is critical. Stick-built gypsum-based drywall material is an outdated cleanroom technology that absorbs moisture and can promote mold growth, the kryptonite of aseptic processing.

Pre-manufactured, container-style cleanrooms struggle with integration in many host building scenarios due to the nature of their fixed boundaries. Once integrated into an existing building, their design is essentially a static structure, which lacks flexibility and limits process expansion.

In contrast to the above two extremes, modular cleanroom installation represents the best of both techniques. Modular cleanroom installation, like the AES Faciliflex Module or AES Faciliflex Express offerings, involves pre-manufactured systems, including architectural and mechanical infrastructure, built to exacting specifications. Modular cleanroom walls and cleanroom ceilings are constructed of fit-for-purpose inorganic materials and coated in a uPVC layer that requires little ongoing maintenance, withstands the harshest cleaning regimens, and does not promote microbial growth. Also, prefabricated cleanroom components undergo verified process quality control checks during the cleanroom manufacturing process, prior to reaching the cleanroom site for installation.

In most instances, existing modular cleanroom facilities can be expanded—entire additions have been added during shutdowns or even long weekends with little to no operational disruption. Modular installation can occur in any host building environment. Unlike stick-built construction, which contributes substantial airborne contamination, modular installation is performed under cleaner installation conditions without the particle generating burden that is common with traditional organic building materials.

UNIQUE DEMANDS FOR AUTOLOGOUS TREATMENT CLEANROOM FACILITY DESIGN

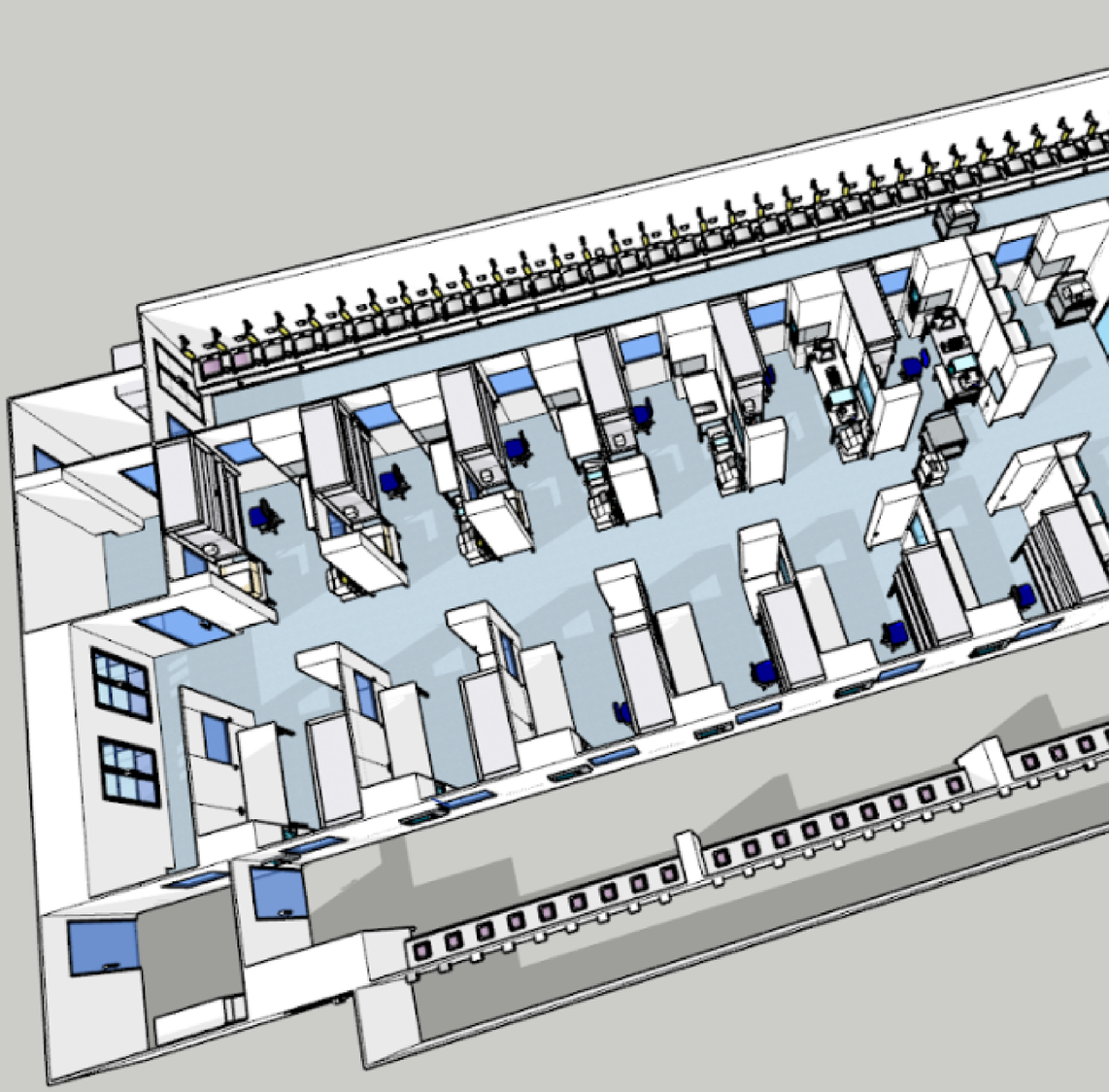
In many ways, the demands on cleanroom facilities were simplified to meet the needs of autologous treatment manufacturing. ATMPs do not induce the need for complex aseptic processing of large batch quantities. In their place are a series of mini -environments (appropriate class BSC hood stations) requiring a Grade C or B background.

The HVAC demands are likewise simplified with the significant reduction of a Grade A footprint, but the control and performance are no less rigorous because the background environment must be compliant in supporting the aseptic processing step. Segregation between workstations is critical to avoid cross contamination. Airflow distribution must not only meet temperature, humidity, cleanliness, and pressurization requirements, but segregation of air flows must support case separation.

Future designs for autologous treatment cleanroom facilities will be driven by the need for faster operational methodologies. Modular cleanroom installation has proven to be inherently faster in terms of design, manufacture, and installation.

The physical properties of modular cleanroom components can also contribute to a higher aseptic standard. Leveraging knowledge and learning can deliver standardized layouts for both autologous and allogeneic manufacturing, further accelerating project execution and, ultimately, speed to market.

Cell and gene therapy manufacturing requires relatively small and defined processes, which preclude the need for the large scale, complex facilities that are typically used in the manufacture of conventional therapeutics. Indeed, the unique nature of autologous and allogeneic operations requires an overall rethinking of the risk-benefit assessment typically utilized when planning a new cleanroom facility.



EVALUATING THE RISK/BENEFIT CALCULATION

At AES Clean Technology, our experience with hundreds of advanced therapy projects reveals that commercialization success centers on a handful of critical capital project planning inputs. None of the items listed are new to industry, but some are lost in the precommercial frenzy of work in an environment with limited resources.

1. 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. A robust commercial forecast (both domestic and global) includes projections and considerations for commercial product, clinical supplies, marketing samples, raw materials, process yields, QC Quality Control samples, FDA retains, stability, revalidations, expiration dating, overages, warehouse, and pharmacy storage capacities. Risk management and contingency factors are also prudent in maintaining supply continuity, which includes ongoing pipeline clinical studies.

This is a challenging task for new clinical projects penetrating into new markets, nonetheless there are many reputable firms who can provide these forecast outputs based on preliminary demand inputs.

As a project's development crosses the threshold from clinical to commercial manufacturing, so does the imperative need for clear projection on patient needs (i.e. Market) versus the ability to supply commercial goods for life saving products. Commercial production requirements represent a higher standard of "current" Good Manufacturing Processes (e.g. localized protection, product traceability, cross contamination controls). With the high unit cost of a newly constructed, regulated facility, it is prudent to right-size a manufacturing operation as the fate of a company's stability and patient health are directly tied to it.

Whether a company makes or contracts the manufacturing supply chain, this will likely be the largest investment/commitment in the company's history. For these reasons, experience has shown the first step to commercial success in building a quantitative plan based on needs and not a qualitative guesstimate. In many instances companies will conduct a "back of the napkin" type of calculation and multiply it by 5X and "go-for-it". This a high-risk approach to patients, company longevity, and shareholders, considering that every multimillion dollar strategic decision will be based on this plan for many years following initial site licensure.

A forecast enables a company to communicate on multiple levels with contractors, suppliers, management and executive teams in rationalizing resources needs, focusing on goal specifics, and negotiating high value contracts.

Also, when a cell or gene therapy clinical program has the advantage of being designated Breakthrough, Priority, Fastrack, or Accelerated by FDA , expectations are clearly documented in the Guidance for Industry for Expedited Programs for Serious Conditions – Drugs and Biologics May 2014, that the sponsor is expected to demonstrate their ability (and responsibility) to supply patients as part of expedited review.

It states, *"When sponsors receive an expedited drug development designation, they should be prepared to propose a commercial manufacturing program that will ensure availability of quality product at the time of approval. The proposal should consider estimated market demand and the commercial manufacturing development plan."*

2. CONFIRM MAKE VS. BUY

WILL YOUR POST-APPROVAL SUPPLY CHAIN BE INTERNALLY OR EXTERNALLY PROVIDED?

- 3-5 year finished goods commercial forecast (current)
- A comprehensive conceptual cleanroom design
- Technical transfer package

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. As the industry moves from biotechnology to cell & gene therapy, the complexity of the science and its manufacturing processes have also increased– along with a greater need to protect intellectual property. With the inherent evolution of these sensitive manufacturing processes, a company's limited access to CMO facilities prevents the company from developing and retaining deeper knowledge of their coveted process.

Cell and gene therapies inherently yield smaller batches relative to established biotechnology products. Smaller batch sizes, in conjunction with the advancement of single use technologies, have induced smaller manufacturing facility footprints, which decreases capital project costs.

Therefore, the Make vs Buy decision becomes a serious consideration for these types of products and should be evaluated early in Phase 3. A conservative plan could 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).

It is imperative to complete a preliminary concept design of a production facility. This will achieve a few needed outcomes: 1) it will unify the team on the understanding of a commercial supply mfg process and project scope, 2) confirm a regulatory filing & quality strategy, and 3) baseline an actionable capital project cost estimate for executive review and consideration.

3. DEFINE/DOCUMENT THE MANUFACTURING PROCESS

HAVE YOU DEFINED YOUR MANUFACTURING PROCESS?

- Automation and/or closed processing
- A detailed process flow definition
- A comprehensive process risk assessment (e.g. ICH Q9)
- A preliminary master validation strategy

The single greatest influencing factor on the design and cost of a new plant is the process design. Designing a plant without this yields a one-size-fits-all, which may not be bad in and of itself, but will certainly prove more costly than a fit-for-purpose design would be.

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 flexibly, and enable product transferability or portability.

Cell and gene therapies are inherently a small batch operation, which further leverages these benefits. A well-documented PFD enables designers to meet clinical, commercial and development product needs based on a necessary capital budget estimate.

'THE SINGLE GREATEST INFLUENCING FACTOR ON THE DESIGN AND COST OF A NEW PLANT IS THE PROCESS DESIGN.'

4. BUILD CROSS-FUNCTIONAL TEAMS

IS A TEAM IDENTIFIED & SANCTIONED?

- Establish a project Roadmap
- A cross-functional team
- A defined project Charter

No external consultants will ever know the technical, operational, or strategic objectives better than a company's internal subject matter experts. Inevitably, a multimillion-dollar strategic capital investment will require many decisions, challenges, and risks and, logically, an appropriate governing forum for goal achievement. 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.

Considering that it takes hundreds of experienced staff (or tens of thousands of hours) to commercialize a product, the sooner these resources are focused on a company plan, the better the chance for timeline success. A general roadmap can provide a visual layout that combines strategic with tactical objectives to guide company wide effort. Its cousin, the Charter, is a one-page tool that defines overall scope, objectives, members, timeline, assumptions, and risks of the project initiative.

Neither roadmaps nor charters are a trivial creative exercise, as both are known to consume many hours due to necessary internal debates that the process will force into being. As tedious as these exercises may seem, they are crucial to building cohesive corporate alignment and serve as a significant step toward focusing resources and avoiding delays.

'WITHOUT THE BENEFIT OF A CROSS-FUNCTIONAL TEAM, THERE IS GREATER RISK TO PROJECT SUCCESS.'

HOST FACILITY CONSIDERATIONS

The building that will ultimately host the GMP cleanroom facility is a critical piece of the puzzle. The cleanroom facility must be properly laid out within the host building such that it can meet cGMP requirements for the flow of materials and personnel. Not only that, but the host building must also be capable of accommodating the expansion of the cGMP area in the event of future growth of manufacturing requirements.

In order for the cleanroom to be fully operational, the host building must be able to support it from an infrastructure standpoint. Critical attributes of a host building's infrastructure include sufficient structural support, electrical capacity, incoming water supply, outgoing waste capacity, utilities for cooling and dehumidifying, dedicated utilities to support processing of the product, and high-speed communications capabilities–just to name a few.

Many existing buildings that are initially considered as the home for future GMP operations are woefully underprepared to provide the necessary infrastructure, so the existing facility must be evaluated for its ability to support the unique and demanding requirements of the cleanroom facility. Not only does the existing infrastructure need to be studied for its overall capacity and quality of infrastructure, but the necessary segregation must be in place to ensure that the cleanroom facility can operate without impact from the surrounding spaces or adjacent businesses. This is particularly important within a multi-tenant facility.

With more than 35 years experience developing cleanrooms within a myriad of host buildings, AES has faced and overcome as ever-growing list of challenges for its clients.

The following are a few highlights that can help to quickly assess whether a host building can support the cleanroom:

Was the existing concrete floor slab designed to support only office space or light duty storage? This may not be sufficient to support the loads of processing equipment or HVAC and utility equipment.

Is the existing overhead structure constructed of wood members or of light duty bar joists? This may not be sufficient to support the weight of utility systems, HVAC distribution, walkable ceilings, and electrical distribution.

Is there sufficient overhead clearance to support the height of the cleanroom plus its dedicated mechanical infrastructure that must be installed above? Some buildings have extremely low clearance, which can create significant impediments to the cleanroom facility.

Was the host building's electrical distribution developed to support only office space or light duty storage? This may not be sufficient to support the intense electrical requirements of a GMP facility.

Is there chilled water, hot water, and steam utilities within the existing building that can be used to serve the cleanroom HVAC systems? Are those utilities at the right temperature, flow, pressure, and quality?

Is the tenant in the adjacent space performing operations that will be detrimental to maintaining cGMP? Are there shared shipping and receiving areas?

And the list goes on...

Not only does the cGMP cleanroom facility need to be engineered and installed for success, but it must be supported by an appropriate host building that can provide the necessary infrastructure that can ensure its performance and also provide for the segregation that will be needed to produce validated products.

CONCLUSION

The ATMP evolution represents dramatic changes for both patient success and the biopharmaceutical industry as a whole. As the cell & gene therapeutic field has emerged, AES Clean Technology has been an active client partner, and we have witnessed how manufacturing needs have evolved in response to the selective demands of autologous and allogeneic methodologies.

As a result, we have seen substantial changes in our industry. Not just how cleanrooms are designed, installed, and expanded, but in the role that manufacturing processes play in the ultimate success of a product. The decisions companies make at the outset of production planning are more important than ever in getting products to patients.

New strategies, from location selection to process automation, need to form at ever-earlier moments in the ideation and marketing planning stages of ATMP product development. Modular cleanroom installation, in particular, is a mature and flexible technology that solves problems and guarantees results.

TAKE ADVANTAGE OF CLEANROOM MANUFACTURING'S STRENGTHS IN CHARTING YOUR PRODUCT'S ROADMAP FOR SUCCESS.

ADVANCED THERAPY MEDICINAL PRODUCT CLEANROOM FACILITIES: A ROADMAP FOR SUCCESS

A PLANNING CHECKLIST FOR CLEANROOM PROJECT SUCCESS

AES Clean Technology has provided comprehensive cleanroom systems to the ATMP revolution from the start. Through experience, we know the "end game" on what high-performing facilities look like, and we also know how manufacturing performance excellence begins long before cleanroom installation begins.

Here are a few key cleanroom capital project tenets AES has learned over the decades that can put your upcoming cleanroom design build project on the road to success:

FORECAST PRODUCT SUPPLY:

Would you cook for a party without knowing how many guests you expect? Knowing the product demand vs. supply is your most important guide to "right size" your multimillion-dollar capital investment. Understanding capacity is fundamental to maintaining the integrity and responsibility of patient drug supply.

DETERMINE MAKE VS. BUY:

Controlling your own process is controlling your own destiny. Does your product forecast allow the option to manufacture in-house? With your own facilities, you can cultivate internal process knowledge and more effectively protect your Intellectual Property. Also, consider that ATMPs generally require smaller production footprints than traditional drug manufacturing–and might be in reach of your early lifecycle capital investment.

KNOW YOUR PROCESS:

Understand the capability of the manufacturing process. A thorough understanding should confirm ability, risk, and opportunities at every step –knowledge that will enable you to drive future process improvement and, in turn, allow you to better plan for a facility that will remain flexible and adaptable to your needs.

STRATEGIZE COMMERCIALIZATION PLAN:

The route from bench to patient might be longer if you do not plan ahead. Minimally, a commercialization plan will guide you from Phase 2 through product launch. Ideally, a robust plan will include the on-going support of clinical pipeline drug product candidates. Define your regulatory strategy from the outset and tie your product vision with flexible planning to be sure you can supply your product to market.

SELECT A HOST FACILITY (CAREFULLY):

Dream big, but practice effective due diligence. The checklist of items above should offer strategic guidance on the selection of your host facility candidate—but there are also practical concerns: Utilities. Infrastructure. Patient supply distribution proximity? Know your footprint needs and potential to expand or scale your facilities. Will your facility be from a standard design or require custom planning? What are the costs and risks? Picking the correct "home" is critical, and many "homes" are not appropriate to host GMP operations.

EXPECT GROWTH:

Change, itself, is the only constant. Change is inevitable. You are in this to win short term and long term. To succeed, both process and facility will need to factor growth into each of the suggested concepts listed above. A solid plan for scalability, adaptability and flexibility is the difference between mere short-term success and long-term sustainability.

ANTICIPATE ADVANCEMENTS:

Science and technology evolve. Quickly. You may not know what will advance, but you know progress will happen. Technology, process and automation will push the product lifecycle to be even faster. The best plans anticipate new technologies and tentatively translate their impacts into facility design, process improvements, and market evolution. Prepare to pivot or prepare topay the price.

ABOUT THE AUTHORS

GRANT MERRILL

CHIEF COMMERCIAL OFFICER

Grant Merrill has been involved with cleanroom design and construction for 24 years. He earned his BS in Mechanical Engineering from Cornell University, and then immediately entered the world of critical facilities and the mechanical systems that support them. After a successful career in the industrial HVAC engineering business, Grant joined the AES team 20 years ago. He enjoys leading his team to deliver complex cleanroom facilities to clients throughout the life science industry.

MITCHELL GONZALEZ

VICE PRESIDENT, PROCESS TECHNOLOGY

Mitchell Gonzalez brings three decades of experience to AES Clean Technology, having worked for both large and small biopharmaceutical companies in the United States and internationally. He earned degrees in Mechanical Engineering Technology and Mathematics and holds certifications in Six Sigma Green Belt and Project Management.

READY TO BUILD A CLEANROOM? OUR EXPERTS ARE READY TO HELP.

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