

Can a Modular Approach to Cleanroom Technology Deliver Flexible Sterile Manufacturing Capacity?

Trista Hager, Vice President of Sales at AES Clean Technology, explores the challenges facing pharmaceutical manufacturers in expanding their cleanroom capacity to meet burgeoning market demand. She discusses how a modular approach to new cleanroom installation can help deliver the flexible sterile manufacturing infrastructure to stay ahead of industry needs.

The sterile pharmaceutical manufacturing segment has been expanding rapidly in recent years and is showing no signs of slowing down. Worth \$899 billion in 2021, the market is expected to grow by more than 50% by 2028, reaching \$1,358 billion by the end of the forecast period.¹

Several drivers are responsible for this strong market growth:

- **An increase in vaccine manufacturing needs:** The successful development of several effective COVID-19 vaccines and the need to vaccinate an unprecedented number of people worldwide has led to increased demand for limited sterile manufacturing capacity. A significant investment in expanding this cleanroom infrastructure by national governments and pharmaceutical companies enabled the rapid roll-out of these vaccines. Since then, companies have begun exploring the potential of the messenger (m)RNA technology platform used in several COVID-19 vaccines to develop new products to tackle other viruses, such as influenza.
- **A rise in the number of biopharmaceuticals in development:** The biopharmaceuticals market is projected to surpass \$566 billion by 2032, growing at a compound annual growth rate (CAGR) of 8.2% throughout the decade.² This is a result of the rapidly rising number of new biopharmaceutical projects in the development pipeline, with 8,000 medicines currently in development, 74% of which are potentially first-in-class.³
- **Advanced therapy medicinal products (ATMPs) on the rise:** Alongside other biopharmaceuticals, ATMPs based on

genes, tissues and cells are making up a growing share of the development pipeline. The market for contract development and manufacturing organisations (CDMOs) specialising in these therapies is expanding rapidly and is expected to reach \$18.8 billion by 2030, growing at a CAGR of 18.8% over the next seven years.⁴

The reason all these developments are driving demand for sterile manufacturing is simple. Due to their sensitivity to degradation in the gastrointestinal tract combined with bioavailability challenges, the majority of these treatments must be administered by injection, rather than any other route of administration. Injection bypasses the body's principal defenses against infection. As such, these therapies require sterile processing capacity when they are approved for the market to ensure they are safe for patients to use.

To meet the future processing needs of all of these therapies, CDMOs and pharmaceutical manufacturers are under increasing pressure to invest in their cleanroom infrastructure. Novel ways to build cleanrooms, such as a modular approach to design and construction, are becoming increasingly important to deliver this new capacity quickly and efficiently.

The Challenges of Increasing Sterile Manufacturing Capacity

Efforts to meet the pharmaceutical industry's growing sterile manufacturing needs are complicated by several issues:

- **The requirements of the products that need to be processed:** Ensuring the cleanroom caters to the target product characteristics is essential to maintain high quality and stability. For example, temperature and humidity control may need to be tightly controlled throughout manufacture and downstream processing for a highly sensitive biologic. Where the production line is being built for a specific large-volume project, this is relatively straightforward. However, as small-volume projects, such as ATMPs, begin to dominate the market, it will be important to take the needs of multiple products into account when designing new lines.

- **The need for flexibility:** Equipment and production line features designed to simplify product changeovers are a key requirement in this new age of smaller-volume runs. Many ATMPs in particular are designed to treat rare or orphan diseases, meaning they have smaller batch sizes and runs. Sterile processing lines need to be flexible to allow them to be easily changed over to other treatments at the end of each campaign. Facilities must be flexible enough to accommodate a change to process equipment or to the room conditions required to maintain ISO classification.
- **Limited factory floor space:** The square footage available for a cleanroom installation may be limited based on various building constraints, so the design must be optimised to accommodate all required functionality within the given area.
- **Integration into existing processes:** New cleanroom infrastructure may need to be easily incorporated into lines and processes previously in place. As such, the equipment must be compatible with the machinery already installed on the line. The isolator technology must also be able to seamlessly connect with surrounding technology. In addition, the new cleanroom may need to be easily incorporated into existing operator working preferences to minimise the need to rewrite standard operating procedures (SOPs) or to retrain team members. Designing a cleanroom that meets these needs can empower operators to carry out their day-to-day activities efficiently, with no disruption.
- **The need for speed:** To meet the industry's present high demand for sterile capacity, many manufacturers are under pressure to ensure that their new lines are designed, installed and validated as quickly as possible. Alternative approaches are needed to achieve this goal within a short turnaround time.
- **Regulatory compliance:** In addition to all of the above, cleanroom environments must adhere to good manufacturing practice (GMP) guidelines for sterile products. In the US, the Food & Drug Administration (FDA)

- classifies cleanrooms from ISO8 (the least strict) to ISO5 (the most stringent) to remain compliant with ISO14644. In the EU, the cleanrooms are categorized as Grade A, B, C or D. Manufacturers producing treatments destined for the EU market must also ensure that their cleanrooms comply with the amendments to Annex 1 of the GMP, in force from 2023.⁵

Drawbacks of Traditional Cleanroom Design

The traditional approach to designing and building sterile capacity is to custom build a new line, planning the layout and features from the ground up to meet the needs of a particular treatment. The line is designed either to fit into an existing space or a new facility is planned to house the equipment. The technology is selected both to integrate with existing SOPs and worker requirements, according to the product characteristics of the project, and each machine is sourced from the manufacturer. Then, the cleanrooms are built on-site using stick-built drywall construction methods.

This approach means that the final cleanroom meets the needs of the existing project and can ensure the line offers flexibility for future product changeovers. However, it comes with some drawbacks:

- **Unpredictable costs:** A custom build, combined with the sourcing of individual pieces of machinery according to the specific needs of the line can mean that the costs are unpredictable until the entire line has been planned and built. Unexpected delays in the delivery of equipment can also increase costs, as the completion of the entire project will need to be pushed back.
- **Long lead times:** The traditional approach to cleanroom design and build can take a considerable amount of time, due to sequential design and construction activities. As such, it can be difficult for CDMOs and manufacturers to be responsive to surges in demand for sterile capacity.

“Cleanroom by committee” makes accountability a challenge: In the traditional design approach, no single entity is responsible for the entire design and build process, making it hard to establish accountability or to address issues with the potential to cause delays. In addition, sourcing equipment from many individual

suppliers complicates the management of the entire project. A large number of vendor relationships need to be handled simultaneously, which can take time and human resources.

Pre-integration of Technologies Can Help

These drawbacks can be mitigated by taking a modular approach to cleanroom design and pre-integrating required technologies before installation in the field.

Modular cleanroom infrastructure is pre-engineered, pre-manufactured in individual modules that are built off-site and designed to be simply installed and locked together on-site for ease and accuracy of cleanroom construction. These modules can come as ready-designed turnkey units for speed and ease of build or can be customised to meet a sterile manufacturer's specific needs.

They feature integral heating, ventilation and air conditioning (HVAC) systems to control temperature, humidity, cleanliness, pressure cascade and containment. As they are fully integrated into the unit, they can control these parameters more effectively, enhancing energy efficiency. Integrated linear LED lighting and controls also reduce energy consumption.

Pre-populated modular electrical raceways and standardised utility connections within each unit simplify installation. Integrated control and monitoring technologies also allow plug-and-play integration.

Modular units come with pre-engineered architecture, featuring antimicrobial materials and finishes applied in a controlled factory setting, ensuring optimum and consistent sterility once installed and streamlining washdown regimes during use. Walkable ceilings can be easily incorporated into the units, allowing easy operational access to critical systems that serve the cleanroom without interrupting operations within it.

Glass walls and prefabricated curtaining can be designed off-site to maximise visibility within the cleanroom environment post-installation compared with the traditional design approach. This can simplify monitoring for workers, making it easier for them to ensure the line continues to operate effectively.

The Value of Modular Design

Thanks to all of these features, modular cleanrooms accelerate project schedules and lend themselves to fundamental and superior

capital investment benefits that traditional methods can't accommodate.

The modular cleanroom systems available today are engineered to accommodate virtually any commercially viable floor plan and a wide range of manufacturing needs. They offer many benefits, including:

- **Greater flexibility:** It is possible to source modular units with special features designed to streamline product changeovers and modifications while in use.
- **Cost-effectiveness:** Manufacturers only need to work with a single supplier that will have access to equipment that offers not only high performance but also reduced cost, cutting the investment required for the entire project.
- **Superior quality:** The nature of the modular approach assures enhanced sterile integrity to other build methods, supporting companies to maintain compliance with increasingly strict regulatory requirements.
- **Expedited validation timelines:** Modular cleanrooms can be designed, installed, validated and put into operation faster than those built using traditional approaches.
- **Clear accountability for design:** There is a single source of responsibility to design, fabricate, install and commission the cleanroom facility. Accountability is clearer, speeding up response should any unexpected events occur during construction to ensure they don't delay completion. Advanced modular cleanroom manufacturers also provide support from dedicated experts post-validation and launch to ensure that the technology continues to offer the highest performance throughout its life.

With these advantages, modular cleanrooms can be an ideal solution to help CDMOs and other pharmaceutical manufacturers equip themselves with the high-performance sterile processing capacity they need to meet present and future aseptic demand rapidly and effectively.

Time to Act to Meet Changing Industry Needs

Given the rapid growth of the biologics sector in particular, sterile manufacturing will

account for an ever greater share of CDMOs' revenue in the future. Taking into account the number of biopharmaceutical projects in the development pipeline, it is unlikely that there will be a slowdown in demand for specialist capacity.



Companies cannot afford to wait to invest in their cleanroom capacity. Working with experts that specialise in modular approaches to design, CDMOs and biopharmaceutical manufacturers can be confident they will very quickly have the future-proofed cleanroom capacity they need to thrive in the future.

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Trista Hager

With over 20 years of cleanroom experience, Trista Hager, brings her extended company knowledge and sales understanding for continued company success. Being able to help clients build facilities that will support treatments of novel lifesaving therapies and pharmaceuticals is the main reason for her continued dedication to the company and why she believes strongly in AES' core values. Trista has been part of the AES team for over 20 years and has held numerous roles including Project Coordinator, Project Manager and for the last 15 years, Project Development Engineer. She has played a key role within the sales team promoting the AES brand, developing regional presence along with being a part of many important projects, including (6) ISPE Facility of the Year Awarded winners.

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