G-CON MANUFACTURING

WHITE PAPER

Flexible Production Platforms for Biopharmaceutical Manufacturing

The Need for Flexible Facility Designs

INTRODUCTION

A paradigm shift in flexible biopharmaceutical production sites and process designs has been recognized in multiple scientific publications and conferences.

The reasons for the flexibility needs are manifold:

⇒ newly evolving drug developments

⇒ changes in process technologies

⇒ transformation of the treatment or patient base

⇒ economical optimization

All of the above require capacity utilization and process flexibility. The large area, product dedicated brick and mortar facilities can no longer meet these requirements which ushers in the need for more versatile and agile facilities in different regions.

With new demands by the industry comes new facility design offerings, which claim to be "flexible facilities," "modular facilities" or facilities that are capable of "manufacturing on demand." In this white paper, we review many types of facility design offerings now available, specifically those labeled modular, flexible, or both.

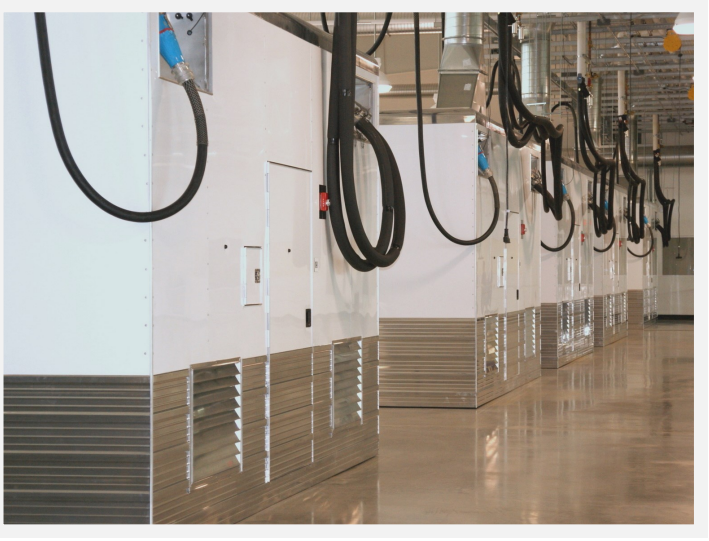

Figure 1: Mechanical side POD view showing utility quick connects as seen from the grey space

FACILITY MODELS EMPLOYED IN BIOMANUFACTURING

With the gradual extinction of traditional brick and mortar facilities, alternative facility designs have emerged, such as, modular container based, modular stick-built, isolator (or containment based) and autonomous cleanroom POD designs (Table 1). All of these designs can be used independently or in combination with other technologies. The requirements of the facility, however, will ultimately determine which platform or platforms will provide the best solution. While each type of platform provider would like to obtain the full facility design, ultimately the choice boils down to the end user's application and its inherent requirements.

WHAT'S AVAILABLE

Facility Design	Description
Brick & Mortar	Traditional facility, usually built for only one product and at large scale. Commonly only used for one product lifecycle. Very dedicated and purpose-built facility design. Centralized HVAC systems in the mezzanine level supply large areas. Containment difficult to manage.
Modular Container	Off-site built container systems, which are interconnected at the final location to form a complete facility. The container modules can be outfitted and designed to purpose. Centralized HVAC system. Significant on-site construction is required.
Stick-Built Modular	The facility is framed out and finished with modular wall panels. The wall panels can be different surface finishes or designs to accommodate custom needs such as room-to-room pass throughs or windows. Centralized HVAC systems in the mezzanine level supplying multiple rooms.
Isolator or Controlled Environmental Module	Built off-site and most commonly introduced into either a cleanroom or at least CNC area. Depending on the system, it can create a good containment option that can be repurposed and easily sanitized. Some systems are connected to a centralized HVAC system. Others could have their own.
Autonomous POD	Off-site built autonomous cleanroom module. Available in various standard dimensions, but can be a custom design. Effortlessly sanitized and decontaminated. PODs are mobile and contain their own HVAC system. Containment is readily achieved.

Table1: Description of facility design options available

MODULAR VS. FLEXIBLE

"Until now, modular facilities have reproduced traditional architecture with regard to embedding utilities piping and HVAC ducts in the interspace between the physical module limits and the suspended ceiling making refurbishment, if required, extremely complicated."

VP of New Product Introduction

Distinguishing between modular facilities and flexible facilities is important, as modular facilities providers typically claim flexibility as well. It is well known that modular facility designs can be deployed faster than traditional facility layouts. However, most modular facilities, once fully assembled are as inflexible as traditional brick and mortar facilities. For example, modular container systems, which are built off-site and ultimately interconnected to create a total facility at the final location, are beneficially compared to traditional sites, specifically the advantage of faster time-to-run. A faster time to project completion has been demonstrated in many projects. However, once built, these buildings are not any more flexible than the brick and mortar facilities they seek to replace. Their "modularity" is lost during the interconnection of the various units.

Similarly, modular stick-built facilities have been labeled as flexible due to the fact that one can add framing and "modular" wall panels within an existing facility. These modular facilities however, are only as flexible as traditional facility designs. Once the panels are put into place, they are not feasibly moved or reusable nor expandable to gain more capacity, therefore provide no flexibility.

DECISIONS TO BE MADE

A decision matrix will determine which of one of the tools shall be utilized for the project and/or for a section of the project. As mentioned, a facility does not necessarily have to be designed with only one of the facility options, but often becomes a hybrid solution of two or three of the options listed. For example, cell therapeutic or antibody conjugate processing happens often in production isolators or other containment options, which are surrounded by a class B environment, which can be any type of cleanroom. Autonomous cleanroom POD solutions are most commonly connected to a stick-built corridor system. No one solution wins the one-size-fits-all approach. Rather, choosing the right design solution depends on the specified purpose. This approach has been utilized for many years in the design of the production processes. End-users moved away from the legacy models to evaluation of the best process equipment choice for a particular unit operation, even if it means multiple vendor use.

"Flexibility is one part of better facility utilization, quality is the other. The quality of the cleanroom system and material gives us the life-span needed."

VP of Manufacturing

Table 2: Advantages and disadvantages of facility design options available

Facility Design	Strength	Weakness
Bricks & Mortar	* Extensive experience level with such facilities * Dedicated product segregation * Large areas * Time-to-run 24-48 months	* Difficult to repurpose * One product lifecycle * High CAPEX * Up to 4 years time-to-run * Inflexible * Large HVAC superstructure * Difficult to decontaminate if necessary
Modular Container	* CAPEX 70-90% of traditional built * Time-to-run 18-24 months * Off-site build-up	* Interconnected to one large facility losing its flexibility at that point * Large HVAC superstructure * Shipping costs * Not scalable
Stick-built Modular	* CAPEX 50% lower than traditional built * Time-to-run 6-24 months * Build into a shell building * Potentially scalable	* Interconnected to one large facility losing its flexibility at that point * Large HVAC superstructure * On-site build-up
Isolator or Controlled Environment Module	* CAPEX 50% lower than traditional built * Time-to-run 12-18 months * Modules are repurposable * Possible to decontaminate * Scalable	* Size limitations make the use of larger equipment difficult * BSL containment limitations * Centralized HVAC
Autonomous POD	* CAPEX 40-50% of traditional built * Time-to-run 6-18 months * Moved into a shell building * PODs are repurposable * Easy to decontaminate * Redundant HVAC system in each POD * Scalable	* Shipping costs * Equipment size excursions require project POD

FLEXIBLE FACILITY PLATFORMS

"The flexibility of facilities is maximized when equipped with single-use technology."

Chief Operating Officer, Biomanufacturing

Flexibility of facilities depends on two major factors: multi-product processing and scalability. Other factors are mobility and the achievement of multiple product-lifecycles. Processing flexibility is often considered in conjunction with single-use equipment technologies. Operating in a single-use manner offers a multitude of technological and economical benefits, one being that the single-use systems represent the first containment barrier. Such capability creates flexibility and the potential of multi-product process opportunities. In a breach incident though, the containment responsibility shifts to the surrounding environment. Therefore, if one desires maintaining the flexibility of the production, the surrounding environment must be easily cleaned and sanitized. This includes the HVAC system and ductwork, which has to be compact and well-characterized to achieve a validated sanitization result. Such can only be achieved when the cleanroom space has dedicated and autonomous HVAC units.

The other side of the coin of facility flexibility is scalability, which allows processes to adjust to the capacity demands needed. Therapeutics facilities must be able to ramp-up fast if drug demand is increasing, and just as easily ramp-down if the demand diminishes. Production processes must still be tightly controlled and within specifications, but at different demand level. Thus, the process and surrounding environment must be robust and able to be duplicated. This "cookie cutter" principle of the production process in a well-known environment applies not only to operations within a facility but to other facilities in other regions of the world.

Figure 2: Inside 24' POD view

THE AUTONOMOUS POD

As noted, the requirements of flexible facilities is cost savings, reduced time to run, having the ability to accommodate multiple downstream processes, scalability of processes and being capable of running multiple campaigns with little time required for changeover. Autonomous cleanroom PODs fulfill all of these needs, since PODs utilize dedicated air handling systems within the mechanical space, as well as independent fire suppression system, appropriate control functions and easy, quick connect systems for utilities hook-up. True flexibility at its best!

Environmental Control: The POD provides a self contained environment, having its own two system HVAC unit with automatic failover for continuous operation and ultimate containment of hazardous material. In fact, the compactness of the HVAC system supports the validation of the sanitization of the system, which meets EU Annex 2 requirements for multi-product use, further reducing cost. The vaporized hydrogen peroxide cycle has be qualified with the PODs and showed sufficient kill rates on bioindicators thoughout. As experienced with single-use processing technologies, POD cleanroom systems deliver fast process turn-around times without diminishing quality attributes.

"PODs can be constructed while engineering is happening, cutting some project timelines from 3 years to 12 months."

Biopharmaceutical Business Development Director

Speed: As a solution to avoid capacity constraints faced by the biomanufacturing industry, PODs make it possible for a facility to run in 6—12 months. The PODs are designed and build off-site, without interrupting the constructive of the building. The work on the building, in which the PODs will be placed and the cleanroom PODs run parallel, saving valuable time. It is easier to pre-configure the site, utility points and connections to the PODs, so everything will be ready to be connected once the PODs and equipment move into place. PODs are run through a Factory Acceptance Test (FAT) at the place of assembly, which abbreviates activities at the delivery point. The cleanroom PODs are ready to use upon delivery. Moreover, flexible facility layouts can be "cloned" easily and built and shipped into place much faster and with less capital needs than before. Facility for country, in country, at a smaller volume design become reality.

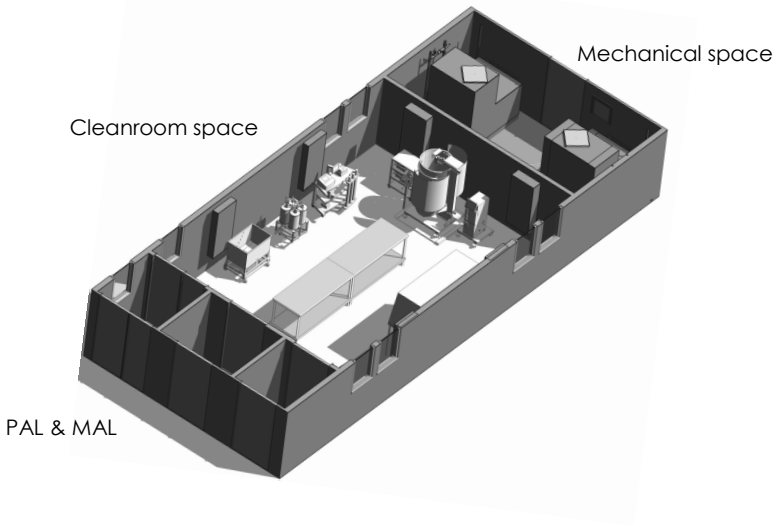

Figure 3: POD layout schematic

Favorable Cost Savings: Financial benefits are realized with PODs, as they allow for operational cost savings in energy, and as mentioned, can be utilized for multiple product life cycles. Being built at a location away from the host facility and connected in minutes upon delivery avoids business interruption and on-site construction management inherent in most other modular platforms.

Figure 4: POD process schematic

CONCLUSION

The terms "modular" and "flexible" are often used interchangeably in cleanroom contexts. However, a close analysis will reveal that most modular facility designs provide no flexibility once installed. Flexibility can be achieved with single-use technology processes. However, flexibility can only be truly achieved if the environment surrounding such equipment is flexible as well.

For example, a company with a product that requires the use of three new bioreactors to meet growing demand may be able to readily acquire the reactors, but attempting to place those reactors in an existing stick built configuration will likely be problematic. Adding a POD can be easily and quickly accomplished. The converse is true as well. If demand falters, dedicated stick built space is underutilized and costly. In PODs, the process can be reconfigured and the excess POD capacity re-deployed.

"PODs finally give us the opportunity to expand, to react to demands, plus place multi-sites to manufacture "in-country, for-country" or avoid drug shortage."

Engineering Lead, Biopharmaceuticals

Single use technology was the harbinger for flexibility. Modular facilities increased that flexibility by the ability of being provided faster than traditional facilities. Now, even greater flexibility is possible with facilities using autonomous cleanroom PODs, that can be scaled to meet demand, moved and even re-used. In this way PODs provide ultimate flexibility. And such flexibility comes at a precipice for drug makers who are being told that selling a drug in a particular region, requires making it there too or otherwise deal with increasing import duties.

Autonomous PODs meet the current and future quality demands of the biopharmaceutical industry and exceed any of the flexibility requirements. A paradigm shift fulfilling a paradigm shift.