WHITE PAPER

G-CON MANUFACTURING

Flexible Production Platforms for Pharma – and Biopharmaceutical Manufacturing

The Need for Innovation in Flexible Facility Designs

INTRODUCTION

The need for a paradigm shift to flexible biopharmaceutical production sites and process designs has been recognized by the industry, including manufacturers, suppliers and regulators alike. The outdated and traditional cleanroom and facility infrastructures no longer meet the industry's current and future needs which are:

⇒ The need for reliable budgets and delivery times for proper capacity planning

⇒ Infrastructures and facilities must be readily deployable; functional in months instead of years

⇒ Cleanroom and auxiliary spaces must configurable and flexible to meet the demands of different therapies and applications

⇒ The ability to scale the facility without interrupting existing processes

⇒ The ability to repurpose a facility, instead of being a single purpose asset

⇒ Cloning of facilities to avoid design reiterations, reduction of varied staff training and abbreviation of qualification periods

These new requirements cannot be met by a single solution, but new innovative solutions are tools in the toolbox that can provide a better solution than legacy approaches that produce subpar results.

While there are several new approaches to cleanrooms, one highly innovative cleanroom infrastructure that is experiencing rapid adoption are prefabricated, prequalified cleanroom units called PODs. These systems can be delivered as standard configuration (Figure 2) or as a project using a POD cluster with multiple subPODs being assembled together (Figure 3).

Cleanroom PODs are fully functional with internal air handling, duct work, automation, fire suppression, controls, etc. all included. The units are built off-site and factory acceptance tested (FAT) before shipment to the client site. This approach ensures that the system operates properly when it reaches the end-user's site. Not only can these systems be designed and built much faster, but they can be built in parallel to the shell host building and equipment, abbreviating the entire construction time (Figure 1).

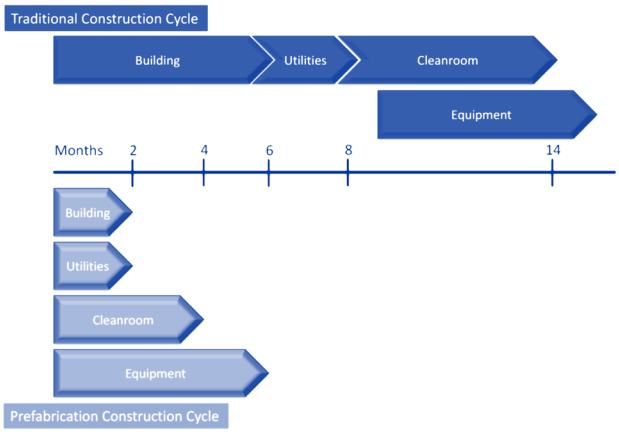


Figure 1: Facility establishment timeline comparison

This option will be considered in more detail with all other available options below.

Figure 2: Single cleanroom POD for cell therapy, lab or filling purposes

Figure 3: Cleanroom POD cluster (14 subPODs interconnected) for a gene therapy application

CURRENT FACILITY MODELS EMPLOYED IN BIOMANUFACTURING

With the gradual decline 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.

Table1: Description of facility design options 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. 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 supply 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 as well. Easily sanitized and decontaminated. Mobile and contain their own HVAC system. Containment is readily achieved.

MODULAR VS. FLEXIBLE

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 for example stick-built. However, most modular facilities, once fully assembled, are as inflexible as traditional brick and mortar facilities. For instance, modular container systems, which are built off-site and ultimately interconnected to create a total facility at the final location, are favorable when compared to traditional sites, due to advantage of a faster time-to-run.

Nevertheless, once built, these constructions 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-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, though, are only as flexible as traditional facility designs. Once the panels are put into place, they are not easily moved, reusable or expandable to gain more capacity, therefore provide minimal flexibility. When any other than prefabricated cleanroom infrastructures are used, all other cleanroom infrastructure becomes a sunk asset, once installed.

CHARACTERISTICS OF THE APPROACHES

The below matrix provides a high-level overview of the strengths and weaknesses of each offering. Hybrid solutions can be used to further optimize the result.

Table 2: Advantages and disadvantages of facility design options available

Facility Design	Strength	Weakness
Bricks & Mortar stick-built	* Extensive experience * Dedicated product segregation * Large areas	* Extensive onsite activity * Unpredictable CAPEX * Unpredictable schedule * Up to 4-year time-to-run * Inflexible * Difficult to repurpose * One product lifecycle * Large HVAC superstructure * Difficult to decontaminate if necessary
Modular container	* Predictable schedule * Time-to-run 18-24 months * Off-site build-up	* Higher onsite activity * Unpredictable CAPEX * Inflexible * Difficult to repurpose * Large HVAC superstructure * Shipping costs * Not scalable
Modular wall panel built	* Time-to-run 6-24 months * Build into a shell building * Potentially scalable	* High onsite activity * Interconnected to one large facility losing its flexibility at that point * Large HVAC superstructure * On-site build-up
Controlled environment module	* Lower onsite activity * Predictable CAPEX costs * Predictable schedule * 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 * Shipping Costs
Autonomous POD	* Low onsite activity * Predictable CAPEX costs * Predictable schedule * Time-to-run 6-12 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 non-standard custom PODs

"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

For example, cell therapeutic or antibody conjugate processing often occurs in production isolators or other containment options, surrounded by a class B environment, which can be any type of cleanroom. Autonomous cleanroom POD solutions are typically 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 have moved away from the legacy models to evaluate the best process equipment choice for a particular unit operation, even if it means multiple vendors.

FLEXIBILITY IS A KEY FACTOR

"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

Flexibility of facilities depends on two major factors: multi-product processing capability 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 economic 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 maintaining the flexibility of production is desired, the surrounding environment must be easily cleaned and sanitized. This includes the HVAC system and ductwork, which has to be compact to achieve a validated sanitization result. Such can only be achieved when the cleanroom space has dedicated and autonomous HVAC units.

Scalability allows processes to adjust to the capacity demands needed. Therapeutics facilities must be able to ramp-up quickly if drug demand increases, and just as easily ramp-down if the demand diminishes. Ramp up can be achieved by duplicating cleanroom environments as needed. This "cookie cutter" principle of the production process would apply not only to operations within a facility but also to other facilities required in other regions of the world.

Figure 4: Inside 24' POD view

DELIVERY TIME AND COST RELIABILITY IS A MUST

The reliability and predictability of project schedules and costs have become more critical than ever. The historic project performance within our industry regarding both indicators has been in desperate need of improvement. In fact, the majority of the surveyed cleanroom and facility construction quote recipients have stated that the upfront promised cost/sq. ft. and/or delivery times were not achieved at the end of the project.

Often times the the actual project costs end up being 1.5X to 2.5X the original estimated costs." The initial costs for cleanroom construction are typically estimated on a cost/sq.ft. basis and include the provision of ceilings, walls, floors, windows and doors. An inexperienced client might assume that the price includes the electrical, mechanical, piping, utilities, automation, which are fundamental requirements for the cleanroom to be functional. Nonetheless, they are often assigned a low base cost or not included in the initial cost estimate provided by many contractors, resulting in change orders and cost increases through the course of the project.

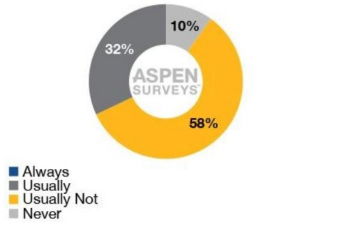
There are also significant additional costs incurred during traditional onsite construction to accommodate the large number of workers and subcontractors, such as costs of temporary parking, material staging areas, gowning areas, insurance requirements, etc. which need to be accounted for. Factors which impact the productivity of the onsite installation team should also be considered, such as subcontractor coordination, weather conditions, and safety protocols and security. Having hundreds of workers located at the construction site for multiple months, adds to the complexity, risk, and cost of a project. Opportunity costs related to construction activities at existing sites should also be considered, since current manufacturing processes may be interrupted or affected.

When it comes to the actual total cost of a project, it is necessary to peel the onion so to speak and add the different cost layers and categories which, when combined, come to a true cost/sq.ft. Once the accurate cost is established, the comparison with other construction approaches, such as prefabricated modular, can be performed. This type of "apples to apples" comparison then allows the decision-maker to make a well-educated decision instead of relying on historical experience or vendor promises.

Project schedule is the other critical variable of a project. Vendor quotes for cleanrooms typically include a timeline for completion of a project. This timeline is then used to plan all the sequential construction, equipment implementation and validation steps. If one aspect of a timeline shifts, the entire project schedule will be affected. When the project is delayed, it can ultimately affect the availability of product to the patient. Therefore, the timelines provided must be as accurate as cost quotes. Speed is also important because it means faster time to market and faster incremental revenue.

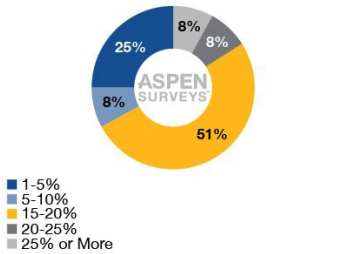
Since speed is a focus when planning a facility in today's environment, the pressure to be able to design and build a site rapidly is of paramount importance. Vendors know this and therefore often quote timelines aggressively, even if not realistic, knowing that schedule changes and delays can later be blamed on a number of factors, including deflecting blame to the client. This is not only bad business practice, but it creates an extremely difficult situation for the client project management team who has to report these delays to their senior management team after making commitments based on vendor promises.

Do onsite construction projects run as planned in terms of budget and schedule?



Aspen Alert Survey, 2019

Have you experienced cost overruns in facility projects? If yes, by roughly how much?



Participant Comment

"In 25 years I have not been a part of a facility capital project that has met cost."

ASQ 721/2019

Aspen Alert Survey, 2019

The saying "time is money" is very relevant when one looks at the value of the drug products manufactured in these facilities. A blockbuster monoclonal antibody batch can have a value up to $ 20-30 million. Therefore, any time delays in establishing a site can have major financial implications.

Cost Comparison 2 x 2000L Facility

Incl. Building, Cleanroom, Utilities, Equipment	Prefabricated	Stick-Built	Modular-Built
Total Project Costs to Construct	$26,497,500	$23,475,600	$25,160,700
Project includes a 45,455 sqft structure for each scenario ($/sf)	$582.94	$516.46	$553.53
Time to Build (in months)	10	21	19
Value of Run:			
Per Batch	$26,000,000	$26,000,000	$26,000,000
Batches/Week	0.67	0.67	0.67
Weeks/Month	4	4	4
Revenue/Month	$69,680,000	$69,680,000	$69,680,000
Value after 22 months from beginning of process	$836,160,000	$69,680,000	$209,040,000
Assume a 40% Net Profit	$334,464,000	$27,872,000	$83,616,000
Depreciable Life	5 – 7 years	8 – 10 years	10 – 15 years
Useful Life	20 – 30 years	8 – 10 years	10 – 15 years
Return on Net Assets:	**12.6**	**1.2**	**3.3**
Net Present Value (NPV)	**$186,096,239**	**$27,210,530**	**$50,429,930**
Internal Rate of Return (IRR)	**26.0%**	**8.5%**	**11.7%**
Payback Period	**0 years**	**1.28 years**	**1.18 years**
Discounted Payback Period	**0 years**	**1.33 years**	**1.21 years**

Assumptions:

Batch Size	2000L
Titer	2g/L
Yield	65%
Grams/Batch	2600
Price/Gram	$10,000
Prod. Reactors	2
Overall 2KL Cycle Time	21 Days

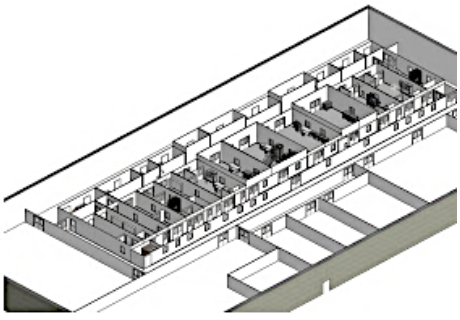


Figure 5: Value comparison of different cleanroom constructions

THE AUTONOMOUS PREFABRICATED POD

As noted, the requirements of flexible facilities are cost savings, reduced time to run, having the ability to accommodate multiple 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 contain dedicated air handling systems within the mechanical space, as well as an independent fire suppression system, appropriate control functions and easy, quick connect systems for utilities. All of this provides true flexibility.

Environmental Control: The POD provides a self-contained environment, having its own HVAC unit and can be designed for containment of hazardous materials. 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. Vaporized hydrogen peroxide systems have been qualified in PODs and showed sufficient kill rates via bioindicators throughout.

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

Chief Operating Officer, Biomanufacturing

Speed: As a solution to avoid capacity constraints faced by the biomanufacturing industry, PODs make it possible for a facility to be operational in 6—12 months. The PODs are designed and built off-site, with minimal impact to the on-site construction activities. The work on the building, in which the PODs will be placed, and the production of the cleanroom PODs run in parallel, saving valuable time. It is easier to pre-configure the site, utility points and connections to the PODs, so everything can be connected once the PODs and equipment move into place. PODs are pre-qualified with a Factory Acceptance Test (FAT) at the place of assembly, which abbreviates activities at the delivery point. Moreover, flexible facility layouts can be "cloned" easily and built and shipped into place much faster and with less capital needs than before. Facilities for in-country for-country production for smaller volumes can become a reality.

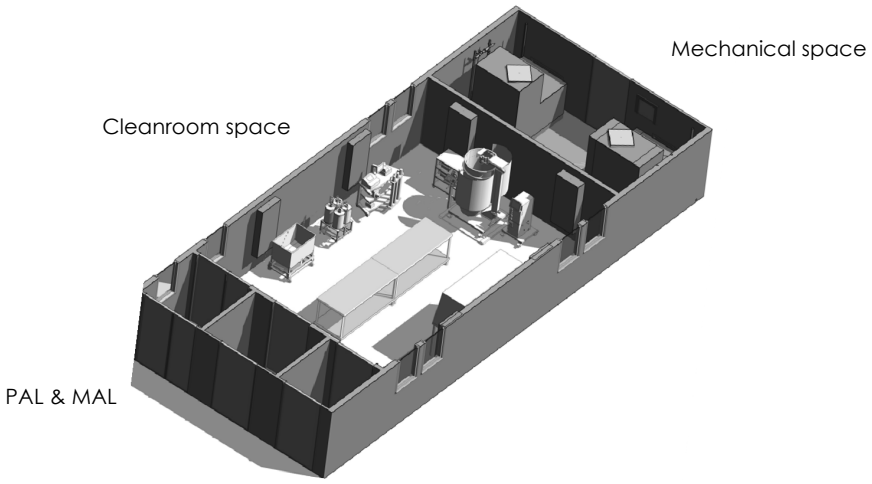


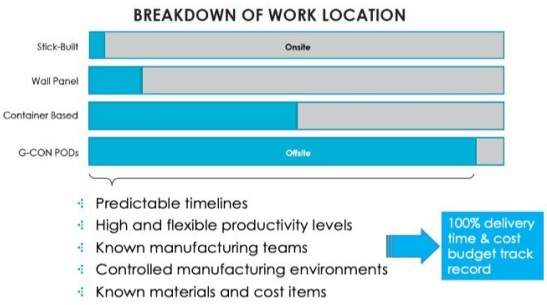
Figure 6: Single POD layout schematic

Favorable Cost Savings: Financial benefits are realized with PODs, as they allow for operational cost savings in energy, and can be utilized for multiple product life cycles. Being built at a location away from the host facility and connected rapidly upon delivery avoiding business interruption and on-site construction management inherent in most other modular construction approaches. Inherent indirect costs, like temporary material, staging, parking, safety and insurances required in traditional construction are avoided, as the units are constructed off-site and the installation crew is a small team who are on site for a short duration.

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

Biopharmaceutical Business Development Director

Delivery and Budget Reliability: To plan capacities to meet demand, the industry requires reliable delivery times and budgets. Traditional design and construction projects have not shown such reliability. Most commonly these projects are delayed by months and the cost runs 30-50% higher than budget. Off-site construction is not influenced by factors that lead to increased cost and time such as weather conditions, head count densities, gowning/degowning, material movements into a site, potential union disputes just to name a few examples. Moreover, the off-site build is much more flexible and if time delays are experienced, time can easily be recovered through overtime or shift cycles. To further reduce the delivery time, standard POD portfolios are being developed so that shipment of cleanroom within weeks with no design phase, can become a reality.



Mobility/Repurposability: Cleanroom PODs are mobile, off-site built, prequalified and then shipped to the customer site. Mobility has multiple advantages, for example, PODs do not have to be permanently installed at any site. They can be installed at a temporary site if the end-site has not been chosen yet. The cleanroom PODs are, therefore, not a sunk asset, but can be moved to the end-site when ready. If manufacturing capacity is needed somewhere else, the PODs can be relocated and if already designed as multi-country unit, can be shipped and used globally. Moreover, PODs can be reused, repurposed as these systems are robust and reconfigurable. If a product lifecycle runs out or the capacity is needed in another therapeutic area, the PODs can be cleaned, sanitized and moved wherever these are required.

Autonomous: Each POD or POD cluster have their own HVAC. With that the POD cleanrooms are autonomous. This is of importance when multiple PODs are used in the same space, potentially for multiple applications. The units create excellent segregation from other units within the same space. For example, a warehouse could be the staging platform for either a multi-tenant or multi-product scenario. Each cleanroom is not interconnected but is autonomous from each other. It also supports decontamination needs, when a cleanroom has excursion, that cleanroom can be shut down and decontaminated without interrupting the entire infrastructure.

APPLICATIONS

Cleanroom POD units can be used in a multitude of applications. Previous installations include:

* **500L fed batch and continuous bioprocessing**
* **4 x 2,000L fed batch and continuous bioprocessing**
* **CAR-T cell therapies**
* **Gene therapies (clinical phases)**
* **Exosome therapies**
* **Viral vector processing (clinical and commercial scale)**
* **Continuous Oral Solid Dosage (OSD) forms**
* **Aseptic compounding and filling**
* **Blow/Fill/Seal filling**
* **Viral vaccine (veterinary application)**
* **mRNA processing (clinical phase)**
* **Continuous API and flow chemistry processes**
* **Egg based vaccine platform**
* **Laboratory application spaces**
* **Transmissible disease mobile testing labs, containment and isolation units**

Six of the top ten pharma companies use PODs for their applications. Cleanroom POD applications have received regulatory approval for commercial production.

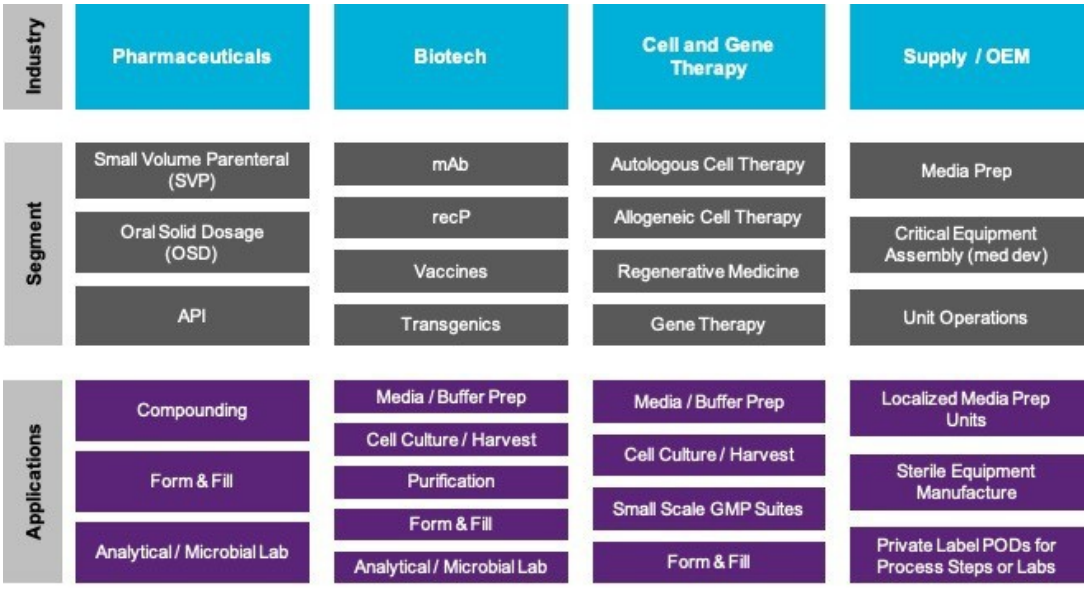


Figure 7: Cleanroom POD application matrix

Bioprocesses

Multiple bioprocess solutions fed batch and continuous processes are all regularly employed in the market today. Since the expression rates in monoclonal antibody processing have become much more efficient, the bioreactor volumes have decreased to 2,000L single use designs with much smaller footprints. Such benefits the POD infrastructure where the unit operations are either segregated or the upstream and some of the downstream process operations are in a ballroom layout. Both designs are available with POD infrastructures.

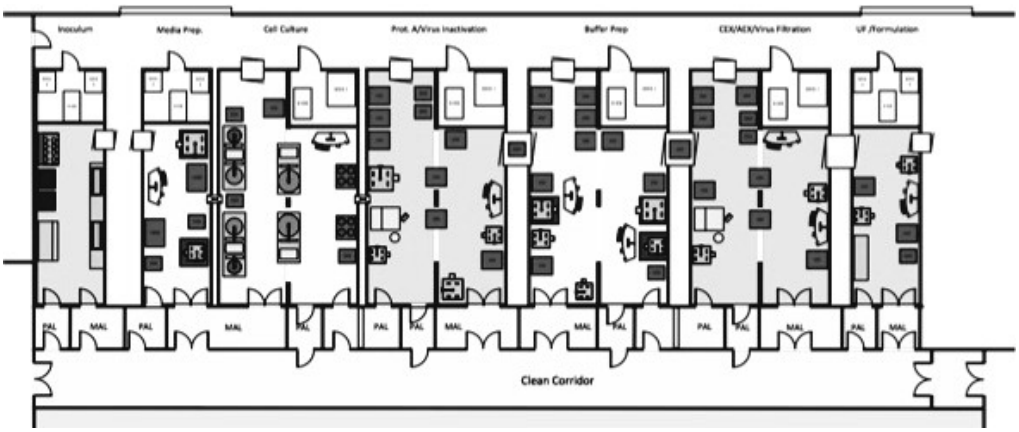


Figure 8: Bioprocess layout with segregated unit operations

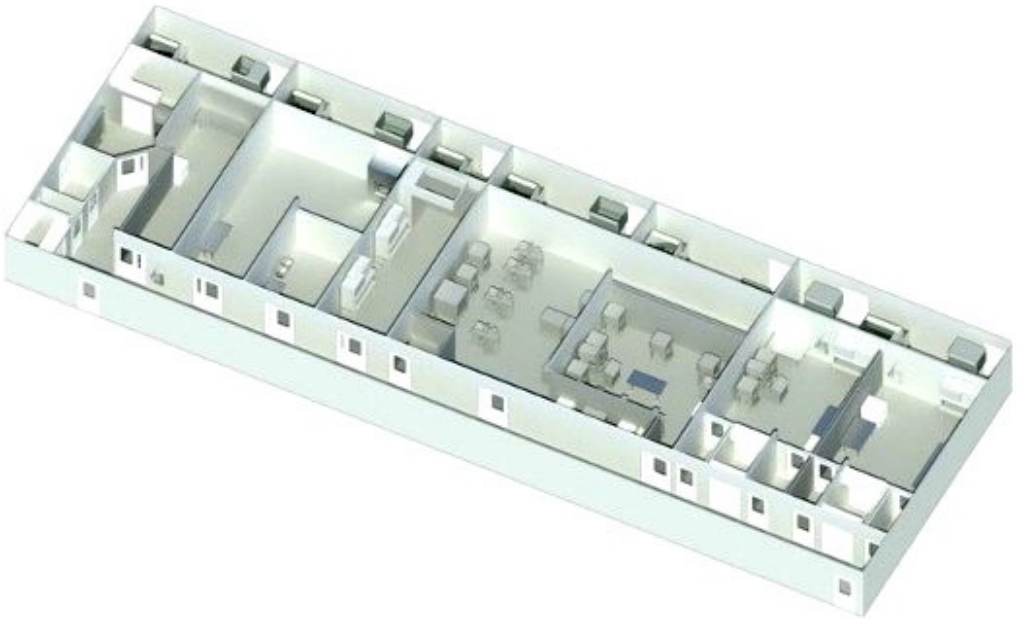


Figure 9: 500L perfusion bioprocess layout with segregated unit operations

These infrastructures are easily scalable or cloneable.

Typically, facilities are designed and redesigned by A&E (architecture & engineering) firms when an end-user asks for a specific requirement. Although the processes do not vary tremendously, the redesign creates billable hours. At G-CON, we believe facilities can be turned into catalogue items and turnkey facility platforms can be created to abbreviate the design and build phase.

The first 4 x 2,000L mAb turnkey facility platform was created together with IPS Engineering and G-CON, called iCON UBERbioFLEX. This platform has the flexibility to run development, clinical and commercial processes either separately or combined in the same structure. The facility consists of 6 x POD clusters within a typical high span shell building. This design creates lower costs (35-45 % of a traditional site) and can be fully built in 12 months.

Figure 10: iCON layout

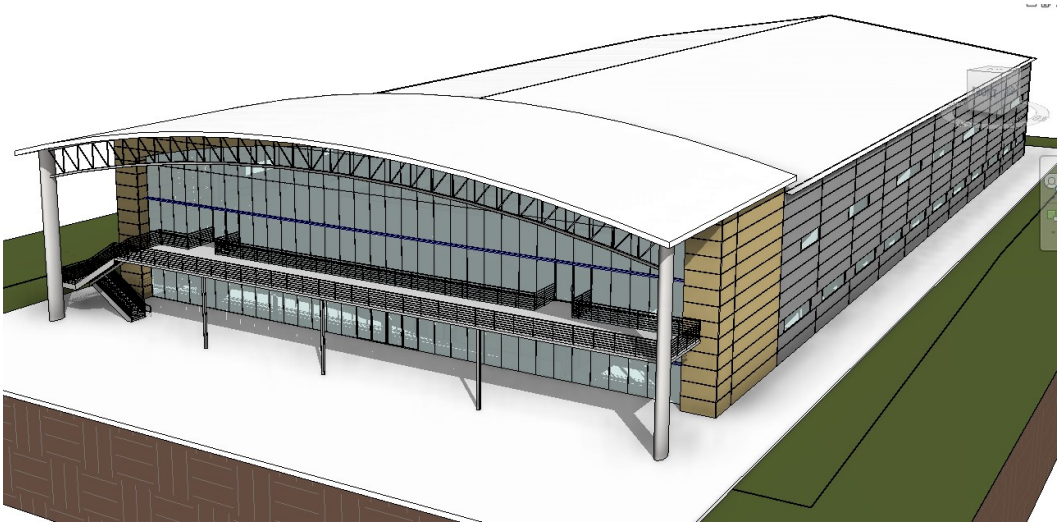


Figure 11: iCON shell building

The shell building, internal infrastructure and equipment is constructed parallel, saving significant time.

Oral Solid Dosage (OSD)

Continuous OSD processing has advanced more rapidly than continuous bioprocesses. With continuous OSD processing, the process equipment has become much smaller without compromising the output of the facility. Continuous OSD equipment also includes advanced process controls and can produce a multitude of different OSD products in the same equipment. The smaller equipment and footprint created the opportunity to place the equipment into cleanroom PODs and even to create a standardized OSD platform and provide capacity much faster.

The PCMM (Portable, Continuous, Miniature & Modular) consortium of Pfizer, GEA and G-CON designed and constructed a fully functional granulation, tablet press and film coating unit within a POD. The megaPOD was built in 6 months and integrated with the GEA equipment in Groton, CT. The manufacturing system is FDA approved and capable of producing up to 500 million tablets a year.

Figure 12: PCM&M megaPOD at Pfizer Groton

One of the primary goals for this initiative was to be able to respond rapidly to emerging capacity needs anywhere in the world with flexibility and cost efficiently.

A comparison showed that a typical traditional manufacturing site required an investment of >$40 million, a 70,000 cb. ft. per process train and 24-36 months to be completed. The PCM&M continuous process system required an investment of ~$15 million, a 30,000 cb. ft. per process train and 8-12 months to be completed.

Such manufacturing platforms are able to be placed in a larger warehouse type building, can produce a multitude of products within such building, and the building can even be shared with multiple tenants producing product and sharing areas such as lab spaces, shipping and receiving, etc.

Development of the next generation PCMM design was initiated with GSK joining the PCMM consortium in an effort to further improved the design by aligning the core competences of the various organizations, but also reduce the height of the equipment to place it into a single high POD. The design has been done to a single high-efficient processing space (Figure 13).

"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

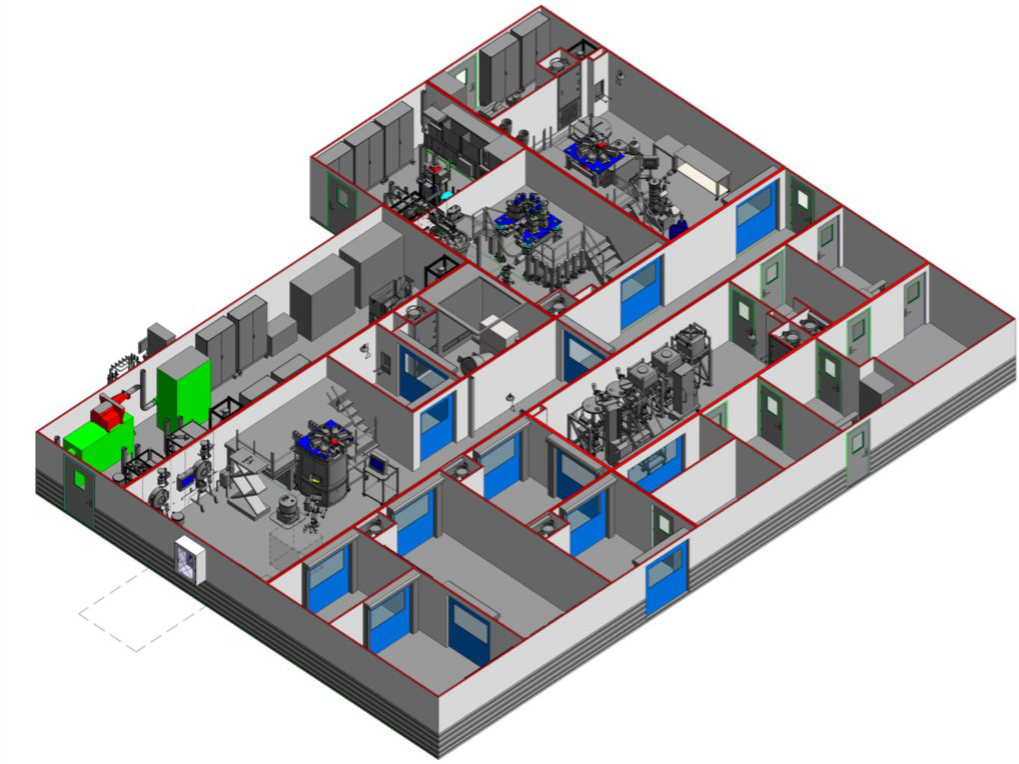


Figure 13: Phase 2 PCM&M continuous OSD process space

This platform can be standardized, eliminating design time and allowing repetitive building by the same team, reducing the timeline and costs to construct the system Moreover, standardization will also abbreviate the qualification/validation timelines.

Vaccines

As with continuous OSD facilities, vaccine manufacturing platforms also require more flexibility to allow a much faster capacity build-up. Vaccine facilities are typically rigid and product dedicated. As an example, flu vaccine facilities are typically single product dedicated and only in operation seasonally and therefore are not efficient. The interconnected processing spaces required does not allow individual segregation.

Designs have been completed for an egg-based vaccine process using 50,000 eggs per day, which could run for flu season and off-season for other egg-based vaccines, since the processes spaces are segregated with autonomous cleanroom PODs (Figure 14).

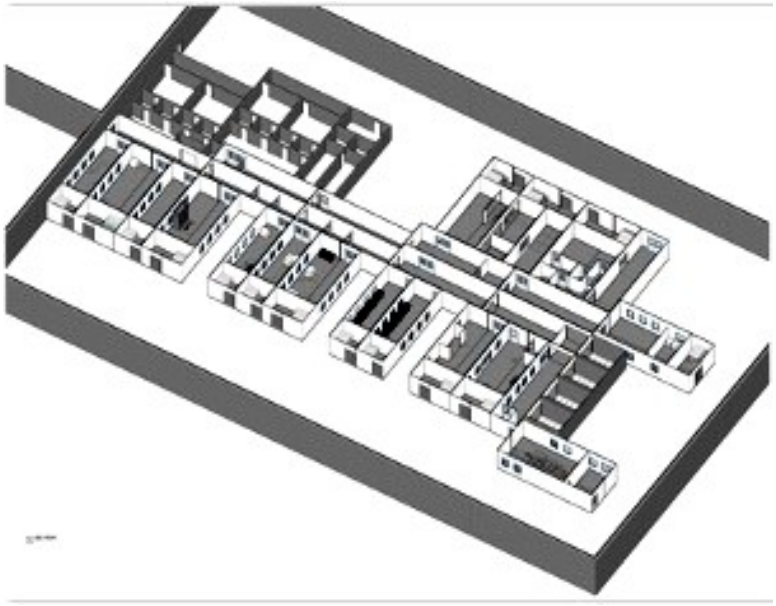


Figure 14: 50,000 egg/day vaccine facility platform

These smaller vaccine facilities can be built within 12 months and placed in multiple regions. The layout depicted is for a classical egg-based facility with the appropriate biosafety level segregation, but it can also be designed for cell culture-based vaccine systems. These smaller vaccine platform designs offer better control regarding potential contamination. An egg-based process is not the cleanest process. If a processing space is contaminated, that space can be shut down and sanitized without interrupting the other processing spaces. Such can only happen with the autonomy of the cleanroom PODs.

G-CON also envisions truck-based vaccine process units, which would be cell culture based, with a purification truck and compounding filling right beside it. The three processing trucks would be supplied by a utility truck, which would supply the necessary electricity, chilled water and other processing needs. G-CON has designed truck-based systems for lab and test lab purposes (infectious disease sampling and testing), that can be converted to vaccine processing spaces. These truck-based systems would not be able to produce large quantities of vaccines as we experience with today's factories but would be able to supply vaccine at a local level without the need for costly and wasteful cold chain transportation. Once a region is satisfied, the trucks can be moved to the next area where needed.

Aseptic Filling

Filling processes and filling capacity are two of the biggest bottlenecks in the industry. Not only for urgent capacity demands but also from a drug shortage aspect, where filling is one of the most common reasons for shortages. Aseptic filling processes are typically large scale, high speed filling lines, requiring vial washing and depyrogenation tunnels. Large scale filling systems are also difficult to control in regard to excursions, contamination, glass to glass contact, breakage, etc.

The industry has begun to move towards smaller systems, isolator or RABS based systems, which are easier to control and contain. The industry is also starting to move towards using pre-sterilized ready to use, nested vials, cartridges or syringes, which avoid the need for washing and depyrogenation.

Cleanroom PODs are finding more utility for aseptic filling systems, as the PODs represent reliable secondary containment and a much more controllable environment. Moreover, filling systems could potentially be pre-installed in the POD and pre-qualified. Therefore, the entire system, filling line and the surrounding environment can be prequalified before it is shipped and installed at the end-user site (Figure 15).

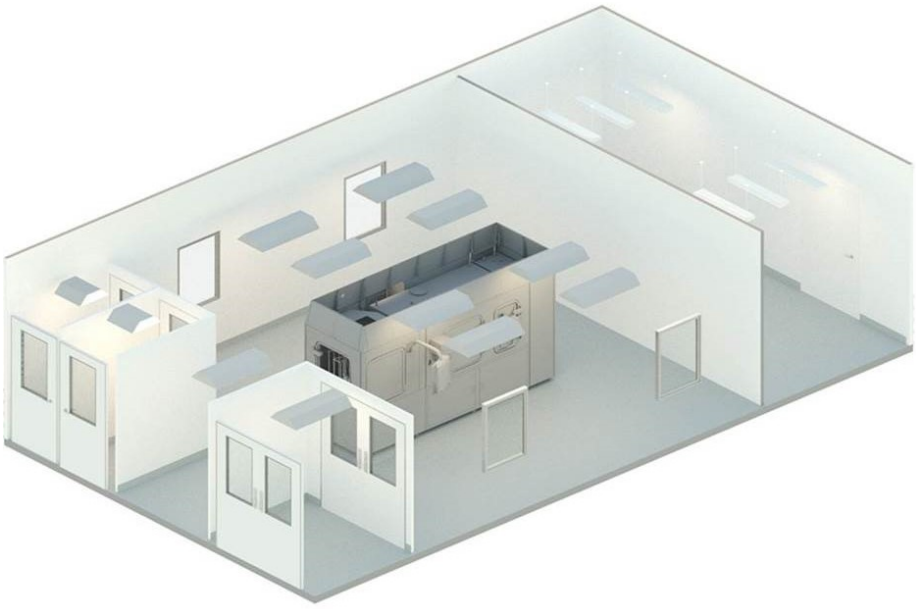


Figure 15: Isolator based, robotic filling line within a cleanroom POD

The smaller and medium capacity filling systems can process 2,000L monoclonal antibody batches, as well as gene therapy and viral vector needs. Typically, the low quantity filling needs and applications such as autologous cell therapies are handled by manual filling, which brings its own problems and can be detrimental when each batch represents a patient's treatment. Filling is most critical step and requires the right equipment, environment and containment. The combination of isolator-based filling and cleanroom POD create the highest level of safety.

Once again, these types of filling applications and filling POD designs can be standardized, and mass produced to be able to deliver the units much faster. For example, G-CON has collaborated with Vanrx, an isolator based, robotic filling system supplier. Together, the companies can jointly supply a prequalified filling line within a

POD in 3 months. And these filling systems can be scaled-out without interrupting existing filling operation. To increase capacity, a new filling POD is simply installed beside the existing one.

Other filling purposes are within the biotech industry, which have different applications and design requirements. Biotech companies are moving to more standardized solutions to be able to implement filling capacities much faster and abbreviate the tech transfer. G-CON has an aseptic filling catalogue with most of the current filling systems integrated into PODs.

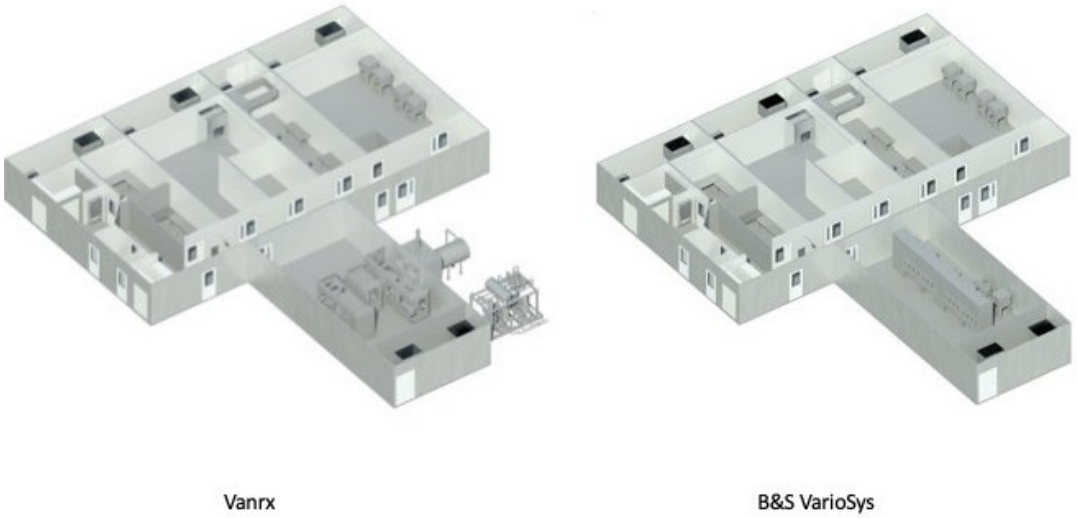


Figure 16: Two isolator-based filling lines within a cleanroom POD and the surrounding PODified support areas

G-CON has supplied a traditional aseptic filling system to the University of Tennessee, which includes a vial washer and depyrogenation oven. This POD system was built in 7 months.

Figure 17: Traditional aseptic filling system within POD infrastructures

Cell and Gene Therapies

Manufacturing capacity in cell and gene therapy is the highest need in the industry These therapies represent a paradigm shift in treating rare diseases and cancer. In the last few years, major breakthroughs have been realized in treating such diseases, with extremely encouraging results. Since many of these therapies are autologous, they are unique in their processing requirements, so current biopharma infrastructures and processing capacities will not meet the requirements of these therapies. New facility and cleanroom infrastructures need to be designed and built to fulfill the need. These therapies also may have distinct differences in their capacity build-up models which need to be considered. And the cleanroom designs must meet the requirements for these process spaces, as well as the capability to rapidly deploy these infrastructures.

In autologous cell therapies, the processed batch is patient specific, as the patient's cells are collected through apheresis and then are processed. This process has to be performed under strict environmental and containment conditions, since terminal sterilization of the final injectable therapy is not possible. Open processing can be done within an isolator or biosafety cabinet within small processing suites. Capacity scaling is performed by adding identical processing suites as needed to the facility. However, this can only be done when each processing cleanroom suite, is autonomous with a dedicated HVAC system and not interconnected with any other cleanroom suites. Scale out has to happen without interruption of existing processing suites.

Often these cleanroom units require unidirectional flow (Figure 18) as strict containment and separation of product, personnel, and waste streams is critical to prevent cross contamination.

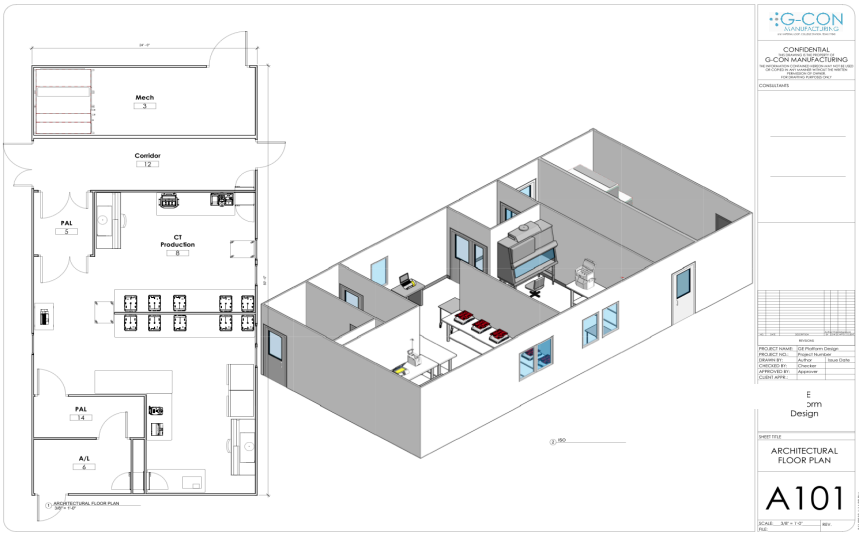


Figure 18: Unidirectional flow cell therapy cleanroom POD

Since the process scaling requirements can change over time based on capacity requirements, the process cleanroom suites often need to be added in phases. Therefore, having a cleanroom process suite design that is clonable is critical. And often, the decision to invest and scale-out may be fast tracked, requiring the additional cleanroom suites to be rapidly deployable. Utilizing a prefabricated offsite autonomous cleanroom POD system that can be pre-qualified in the factory ensures that the units will be fully functional once installed, reducing the time required to start up the new suites. Every day counts to the patient.

Gene therapies are typically batch based and can provide doses for multiple patients, similar to all other medicinal products manufactured within the industry. Therefore, the volumes in gene therapies (and viral vector processing) are larger scale as is the cleanroom and facility infrastructure required for manufacturing these therapies. These infrastructures can be designed as individual unit operation suites connected together or as a more open ballroom design. In both cases multiple cleanroom PODs are interconnected to establish the cleanroom spaces as shown in Figure 19.

Figure 19: Gene therapy fourteen POD cluster

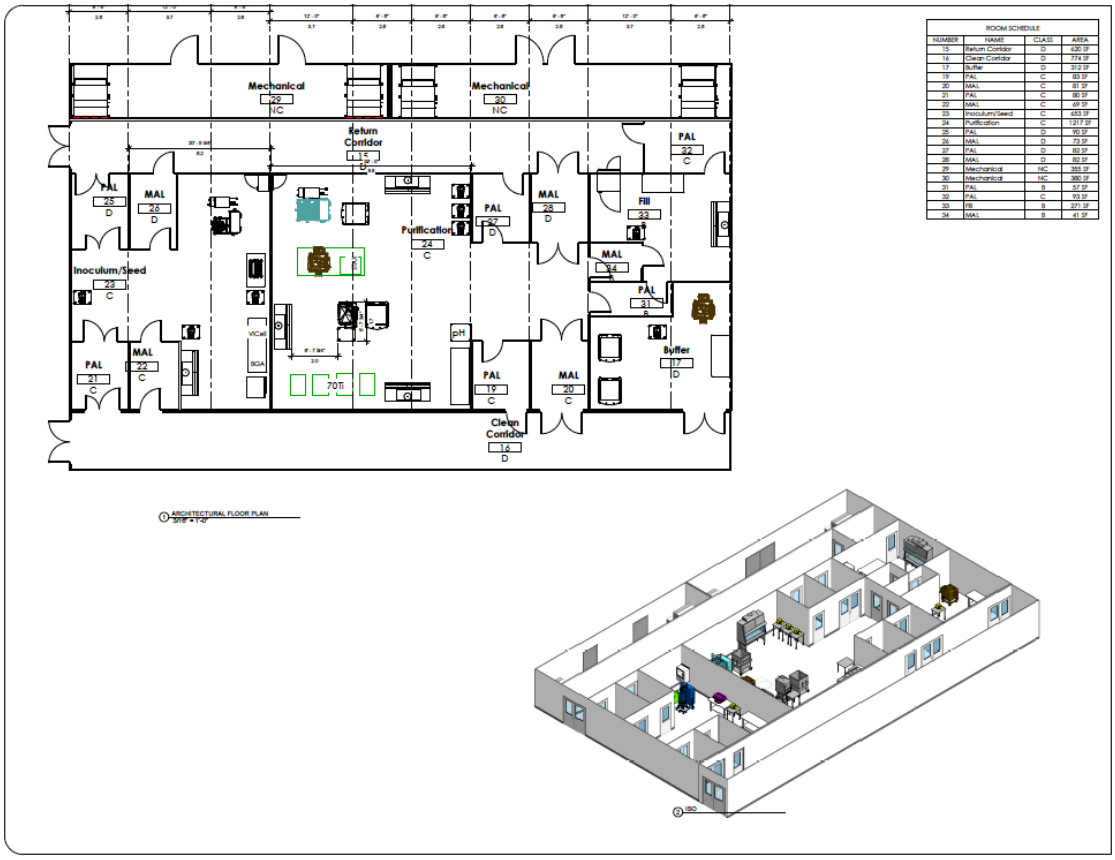


Figure 20: Small scale gene therapy POD cluster

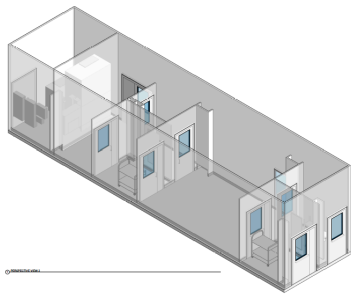
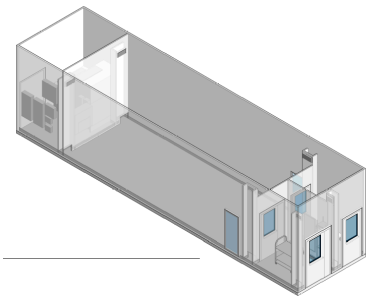
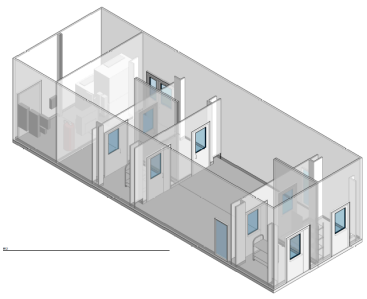
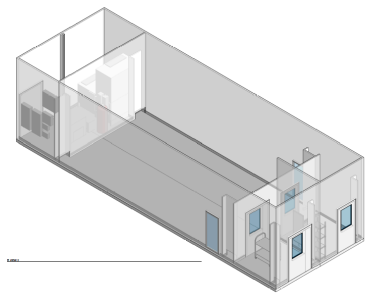
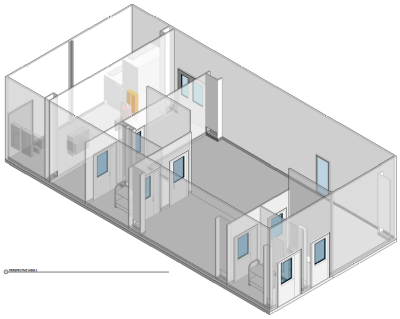
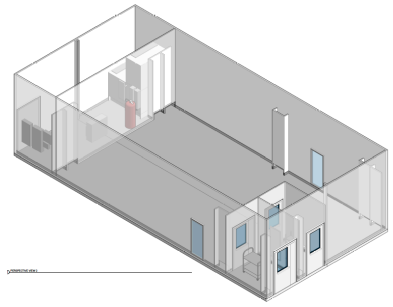
PRODUCT PORTFOLIO AND VISION

G-CON has developed a large portfolio of cleanroom PODs for various applications in order to supply the optimal cleanroom design to the end-user. The key elements, critical to cleanroom infrastructures, including high quality, cGMP compliant designs, delivery speed and predicable costs are inherent to every G-CON POD design. In order to maximize efficiencies related to delivery speed and cost reduction, G-CON's vision is to use a two-pronged approach to serve our clients in an even more optimal way. This includes driving our clients towards a Standard POD design approach and providing full turnkey POD-based facility solutions through our *i*CON platform with IPS Engineering.

Standard PODs

G-CON has six standard cleanroom PODs within its portfolio. These PODs are fully designed, allowing the PODs to be mass produced. Such an approach will bring the delivery time down to 3 months with the ultimate goal of being able to maintain a stock inventory*. With mass production of standard PODs will lower the overall costs even further.

Table 3: G-CON's six standard PODs

Size	Unidirectional flow	Bidirectional flow
12' x 50'		
17' x 50'		
24' x 50'		

*Any changes to these units will bring the price and delivery time up, therefore it is advisable to stay within the standard design.

The standard cleanroom POD range covers a large variety of applications, especially cell therapy and laboratory applications, as these units can easily accommodate the processes within the cleanroom space. The standard PODs can also be used for bioprocessing unit operations and interconnected or for support operations. The important benefit of the Standard POD portfolio is that the delivery times are fast and reliable and the pricing as it is fixed.

Turnkey Solutions

Not all applications will be amenable to using the Standard POD portfolio as sometimes there is a need for larger, application specific turnkey solutions. A good example is the 4 x 2,000L bioprocessing *i*CON platform. This turnkey platform facility solution is pre-designed and therefore can be constructed much faster. The shell building is a pre-engineered free-span building system, which is much faster to build, more economical, and with more flexibility. This type of building can be used for multi-tenant or multi-product purposes, as long as autonomous cleanroom infrastructures are utilized. The important factor of turnkey solutions is the design time abbreviation, but also the ability to clone the facility at multiple sites. Once a turnkey solution has been designed and built, it is a known entity, and the entire design does not need to be repeated for future sites qualification and validation protocols, procedures, and training activities can all be leveraged, based on the original turnkey site. Such an overall turnkey platform facility can achieve much higher efficiencies with more predictable outcomes.

We believe a turnkey facility platform approach can be applied to various process applications including vaccines, recombinant proteins, aseptic filling, oral solid dosage forms, cell and gene therapies. The process footprints are shrinking and the variability between manufacturing will continue to be reduced. Turnkey platform solutions can be designed and used without going through lengthy and costly design reiterations project after project. This will create a much faster deployment of these facilities at lower costs, as well as the opportunity to make capital investment decisions later than typically experienced.

Learning and innovation go hand in hand. The arrogance of success is to think that what you did yesterday will be sufficient for tomorrow.

William Pollard

Standard POD and turnkey infrastructures align with the needs of the industry to lower capital investments and gain predictability in capacity build-up. The old methods and approaches to facility design and construction no longer work. New and innovative approaches are needed to be able to serve the industry and the patient!

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 little to 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 in order to respond to changes in market demand. To gain this flexibility G-CON developed autonomous, prefabricated, mobile cleanroom units called PODs. These units can be built as a single cleanroom POD or POD cluster for larger processing spaces.

The benefits of PODs are many, but as an 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 into an existing stick-built configuration will likely be problematic. Adding a prefabricated cleanroom PODs can be easily and quickly accomplished. The converse is true as well. If demand falters, dedicated stick-built space is underutilized and costly. With PODs, the process can be reconfigured and the excess POD capacity re-deployed.

Single use technology was the harbinger for manufacturing flexibility. Modular facilities further increased that flexibility by providing manufacturers with the ability to design and build faster than traditional facilities. Now, even greater flexibility is possible with facilities using autonomous cleanroom PODs, that can be scaled to meet demand, relocated, and even re-purposed. In this way PODs provide ultimate flexibility. And such flexibility comes at a critical time for drug makers who are being told that selling a drug in certain regions of the world, require that they manufacture locally or otherwise deal with increasing import duties and government restrictions.

Autonomous, prefabricated PODs meet the current and future quality demands of the biopharmaceutical industry and can help manufacturers meet their increasing flexibility requirements – using a paradigm shift to address a paradigm shift.

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