The Evolution of Planning, Design, and Engineering — Flexibility Takes Center Stage

Maik W. Jornitz and Sidney Backstrom

In the lifecycle of pharmaceutical and biopharmaceutical commercial manufacturing, the one constant has been change. During the “blockbuster” years, large, purpose-built facilities were the norm, featuring 10,000-L bioreactors and other reusable stainless-steel process equipment. More recently, improved expression levels in mammalian cell-culture processes and growing implementation of single-use process technologies have allowed the biopharmaceutical industry to evaluate smaller cleanroom infrastructures in facility design projects.

Also driving demand for smaller, more flexible, manufacturing facility designs are the need to produce in-country/for country and advances in biosimilars, which require multi-product processing capabilities. Smaller facilities may provide enhanced containment required for processing highly potent compounds, or the special aseptic filling and processing needed for cell therapy production. Smaller volume filling has also created opportunities for new aseptic processing technologies (e.g., pre-sterilized container systems and robotic filling in isolators). These systems are so compact that they may be “drop shipped” within a prefabricated environment, and rapidly deployed.

As modular facilities replace traditional methodologies, architecture and engineering firms are embracing this new technology. Moreover, modular companies are collaborating, which could signal mergers and acquisitions in this space, similar to what has occurred in process equipment in the past. This article examines the changes now taking place, and what the future might bring.

Maik W. Jornitz* is president, mjornitz@gconbio.com, and Sidney Backstrom is director of Business Development, both at G-CON Manufacturing, Inc.

*To whom all correspondence should be addressed.
Cleanroom Design

The process and the facility switch places
In facilities, single use, product-dedicated designs have given way to reusable, multi-product designs, while process equipment design has moved in the other direction, from multi-use to single-use (1). A facility cannot be considered flexible just because it uses single-use process equipment. If the layout of the facility does not allow easy access or movement, the potential benefits of flexible process equipment will be lost (2, 3, 4).

For example, if a cleanroom space is built to house one fermenter and one tank with no allowance for other equipment or additional personnel, and the required ductwork is interconnected into the cleanroom from the larger facility, a change as small as the addition of a second fermenter or tank could result in having to rebuild the entire room.

If, however, the cleanroom were built with its own air handler and the process required the addition of another fermenter and tank, a second cleanroom could be easily added without interrupting the existing process. In the first example, the arrangement is static—dedicated to the product produced at only one scale. Once more product is needed, or the process is changed, the layout no longer works.

In the second example, the facility was built with flexibility in mind, so a change in the process required only a small addition, rather than a design change. Such an approach represents the next generation of cleanroom systems, which are not interconnected, but are designed to be autonomous units (3, 5).

The kind of progress being seen in cleanroom and facility designs today embodies the goals of FDA’s 21st Century Initiative (6), which called for “A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high-quality drugs without extensive regulatory oversight.”

Flexible facilities—past, present, and future
For years, facilities were complex, lengthy, and costly construction projects. The question of when to invest in such product-dedicated facilities required years of planning and seven- to eight-figure capital budgets. The first generation of modular container-based facilities was designed to be more flexible than traditional large-scale plants, but in the end, they were just as rigid as the designs they replaced (7).

Advances came when modular panels were incorporated into the design. These systems proved to be more flexible than the container-based designs and could be erected in a shorter period of time. If expansion is required, wall panels could be removed and added to expand the overall layout.

In most instances though, this means that the existing cleanroom areas and processes are interrupted, and the entire cleanroom space will need to be rebalanced and perhaps additional HVAC added or modified after the renovation. In addition, the cleanrooms must be built on site, interrupting manufacturing and requiring resources for management, engineering, and security. Even so, the modular panel structures offered multiple advantages over traditional brick-and-mortar facilities and first-generation modular designs (5, 8).

The latest generation of modular infrastructures, prefabricated cleanrooms, are available in different sizes and for a number of different purposes, from controlled non-classified lab enclosures to biosafety labs. These systems are built entirely off-site, factory acceptance tested there, and then shipped to the ultimate host facility.

Once there, simple connections to water and power are made, supplying the internal cleanroom process piping. Off-site prefabrication avoids all of the cost
and inconvenience of the former method and the units can be installed in days, instead of months.

In one example of a cleanroom project, use of such facilities reduced labor requirements by 8000 hours. It also improved worker safety, because the work was performed at ground level within an environment with plenty of space and supervision.

Offsite-built modular cleanrooms do not require laydown or dedicated work areas as is common for onsite built rooms. For some of the stick-built cleanrooms, laydown areas for materials can often be as much as the size of the ultimate cleanroom.

**All modular designs are not created equal**

The latest modular facilities are not like the old container-based designs, and they are not assembled to an entire facility, which makes these more flexible, relocatable, and repurposable.

Current cleanroom units are equipped with their own HVAC systems, which not only makes them autonomous from the host facility but also means the ductwork is compact and avoids the leakages and pressure losses that can be experienced in convoluted, interconnected ductwork for stick-built systems.

These prefabricated cleanroom units can be built in parallel to the shell/host facility and process equipment, halving construction time in some cases, compared to other options. One of the first manufacturing facilities to use the prefabricated approach, for an oral solid-dosage application, received the 2016 Facility of the Year (FOYA) award for Equipment Innovation (see **Figure 1**) awarded by the International Society for Pharmaceutical Engineers (ISPE)(8). This facility, which can be used for small lot production all the way up to 500 million tablets per year, was designed and built in 18 months, saving two or more years. The total cost for the facility and major process equipment was approximately $15 million instead of the expected $40–60 million (9, 10). In addition, the overall footprint was reduced by 60–70% in comparison to traditional settings. Should the product lifecycle of the product to be manufactured end, the whole facility can be repurposed and/or moved to another location (11).

**Supply chain benefits**

The facility can also be standardized and cloned as a platform approach for in-country/for-country purposes. On the production side, the facility enables the manufacturer to produce on demand instead of based on forecasting, which will lower product inventory and reduce the risk of product expiration. And additional unit operations such as coating and encapsulation can be added without interrupting the existing structure.

These modular facilities can be placed into modest shell buildings around the globe. These shell facilities can then hold additional modular facilities for one or several companies. In the latter example, companies can share administrative resources such as using the same quality control, purchasing, operations support, etc. In either case, cleanrooms are
deployed faster for new product production or product scale up. Resources are more efficiently used. Both will lower the typical operating cost burden, because the clean space is built around the process.

While the advances in modular technology are apparent, what is also clear is that these modules will become the building blocks to standardized platform approaches for well-defined processes. A good example of this is the downstream process for a typical monoclonal antibody (mAb) (12).

Each mAb typically undergoes multiple chromatography steps, viral inactivation, and filtration before finally being formulated and filled. The process itself is well defined and well known, which has been taken advantage of by single-use process equipment suppliers. These suppliers have created single-use process unit operations that can be interconnected to a larger process stream.

These unit operations can be placed into cleanroom containment systems and once again interconnected to an entire facility layout. In the past, it would be left up to the customer and its architectural and engineering (A&E) partner to design the environment around that process step. The result would be significant man hours (engineering and construction) and expense and a custom-built enclosure. This approach begs the question: If the step, the scale, and the equipment are the same, can’t the enclosure be the same? And if the enclosure is the same every time both in terms of size, equipment, and materials of construction, wouldn’t that lead to a shorter time to validation?

With pre-fabricated modules designed with specific process steps in mind, in the near future, process equipment vendors may develop and sell enclosure options for each process step that can be customized to fit the customer need. Thus, in addition to providing the turnkey solution for a particular process step, process equipment manufacturers will also provide the enclosure around the process equipment and thus provide a true integrated turnkey solution, which will greatly abbreviate the current lengthy design phases and lower the cost of facilities. Facilities, such as the process equipment inside, will become reusable commodities. Conceptual design costs would also decrease substantially.

One modular equipment supplier has already partnered with an A&E firm to generate a standardized 50,000-egg-per-day vaccine facility. That same vendor has worked with another A&E firm to design a standardized 2000-L mAb site as well. Bioprocesses of multiple types and volumes can potentially become a catalogue item, instead of being reinvented over again.

**Meeting the aseptic filling challenge**

Smaller volumes within bioprocesses, the need for more robust containment, and new therapies have led to new, compact fill line designs. These systems utilize automation, robotic fill arms, and pre-sterilized container systems, which avoid human interventions.

Because these systems are compactly designed within an isolator, they can be prequalified within the supplier site and gain the final qualification at the end-user site. The next step in the evolution of flexible aseptic processing and filling will be the partnering of the filling line manufacturers with modular companies to provide turnkey filling and enclosure options that can be delivered together. This approach will ease the integration burden and shorten the timeframe for delivery and operation of filling equipment (see Figure 2).

With the first barrier, the isolator, around the fill line, and the prefabricated cleanroom as the
second barrier, compact designs for both, and the possibility of sanitization with vaporized hydrogen peroxide, filling can now stop being the most critical step in the manufacturing process and become a robust and reproducible process step assuring a high level of product quality.

Collaborations between modular companies that, in the past, might have seen themselves as competitors, are now being seen. Modular equipment vendors are starting to carve out their own niches (e.g., modular built offsite versus onsite built panels), and some are starting to work together. At least one major supplier of offsite built cleanrooms has included modular panels in some of its latest designs. Those developments promise to drive further innovation and cost competitiveness in this space.

Modular challenges
Whenever modular options are brought up, they inevitably lead to the fallacious question: “What is the cost per square foot?” This figure is only the tip of the iceberg. The total cost of ownership must be considered. Not surprisingly, low-cost vendors can provide enticing quotes, but the prospective owner must dig into the quote to see what is really being provided. The prospective owner needs to consider whether the option will be a turnkey solution that will operate efficiently over the lifetime of the product being produced as well as what the value of that enclosure is after the product lifecycle has come to an end. Table 1 reviews some of the parameters that should be considered in capital projects.

New opportunities for facility design
In short, facility design requirements are evolving, just as bioprocess technologies did as they moved from stainless steel to flexible and agile single-use process technologies (4, 13). These innovative technologies have created new opportunities for facility design, and modular solutions offer potential benefits in boosting flexibility. Today, more major pharmaceutical companies and A&E firms are recognizing these benefits.

The future can be seen in facilities such as Amgen’s new biopharma facility in Singapore, which uses modular technology to achieve a 60% reduction in size with the same throughput as a traditional site, and a five-fold reduction in energy consumption. More examples like this are sure to be seen in the future.

The modular approach also promises to change aseptic filling and processing, which has become an Achilles’ heel for the industry, and a source of product quality issues and shortages, into a robust and reproducible operation.

References
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personnel needs</td>
<td>Does the facility option require owner personnel on site during the build? Construction personnel needs at the site, including supervision and security are often not considered or underestimated. From a safety standpoint, if the personnel density allowance is reached, the project timeline can be adversely affected.</td>
</tr>
<tr>
<td>Design time and costs</td>
<td>Build-in-place options often require redesigns of available space leading to significant engineering, permitting, and construction costs. Off-site built modular options are pre-engineered and reusable leading to significantly less costs in this regard.</td>
</tr>
<tr>
<td>Construction site space</td>
<td>Laydown area larger than the cleanroom space is needed in on-site built options. It is not uncommon that such space is as large as the actual cleanroom space. Off-site prefabrication reduces the space required.</td>
</tr>
<tr>
<td>Validation costs</td>
<td>Offsite built modular systems utilize reusable designs that lead to a more streamlined regulatory review. Onsite built systems are typically custom leading to no such streamlining.</td>
</tr>
<tr>
<td>Superstructure and mezzanine levels</td>
<td>Traditional sites require large mezzanine areas to run miles of process piping and ductwork. This is space, and the cost of the HVAC system and piping needs to be added into the overall project cost calculation. In offsite built options, compact and decentralized air distribution systems reduce the space needs and the need for separate contractors to run such ductwork and piping. In addition, the more compact and contained ductwork reduces the possibilities of leaks and pressure losses leading to a more efficient system.</td>
</tr>
<tr>
<td>Quality materials</td>
<td>The costs of low quality components generate risk of not meeting the required quality standards on a short-term and long-term basis.</td>
</tr>
<tr>
<td>Scalability</td>
<td>Future manufacturing needs to be considered at the outset to determine whether the chosen option allows for scaling without interrupting the existing process. The costs of production interruptions should be accounted for when making facility design choices. If each cleanroom enclosure is autonomous, scaling up without interruption is possible.</td>
</tr>
<tr>
<td>Time to first product run</td>
<td>How fast the facility can be deployed is a crucial factor in the facility decision. Days lost in product manufacturing leads to lost revenue for products with a limited life. The potential for such losses should be considered in the decision making process.</td>
</tr>
<tr>
<td>Depreciation</td>
<td>Onsite built options must be depreciated as a long-term capital asset. Offsite built options that are moveable can be considered equipment and therefore depreciated on a much shorter schedule. In the latter example, a 5- to 7-year depreciation is typical compared to 30–40 years for long-term assets.</td>
</tr>
<tr>
<td>Insurance</td>
<td>Onsite built options require construction insurance and bonding, which can add significantly to the cost of the project. Offsite built do not require such.</td>
</tr>
<tr>
<td>Sanitization</td>
<td>Cleanability of the options should be considered at the outset. An area that cannot be properly cleaned may lead to shutdowns or product contaminations. Some options use gypsum board, plywood, etc. The cleanliness of these options is questionable, especially long term, as cleaning agents can deteriorate such finishes over time.</td>
</tr>
<tr>
<td>“Repurposability”</td>
<td>Can the facility or production area be used for any other purpose when the product lifecycle has come to an end? If the cleanroom can be repurposed when the product lifecycle ends, the efficiencies are apparent.</td>
</tr>
</tbody>
</table>