The changing Environment of Facility Planning, Design and Engineering – Flexibility being a Key Attribute

Maik W. Jornitz, President, G-CON Manufacturing Inc.,

Overview

Increasing expression rates in mammalian cell culture processes and the rapid implementation of single-use process technologies, encourage the biopharmaceutical industry to evaluate smaller footprint cleanroom infrastructures, respectively facility designs. The need for these smaller, but more flexible, manufacturing facility designs were accelerated by the requirement to establish in-country/for country manufacturing and by biosimilar developments, which require multi-product processing capabilities. Furthermore, therapies are changing and highly potent components necessitate robust containment and cell therapies the protection of the purely aseptic process. The call for higher flexibility and agility, besides rapid deployment and shorter time to run, generated a favorable view and adoption of innovations within the manufacturing area designs and cleanroom infrastructures. Traditional systems are getting replaced by more flexible and robust design and material options. Modular biomanufacturing facilities are adopted to gain the required flexibility and shorter time-to-run. To the benefit of the industry though, modular designs and materials evolve further, creating an enhanced toolbox of facility design choices. The evolution is not stopping at the materials and construction of the modular cleanroom infrastructures, but enhance further to standardized or platform systems, which can also reduce design timelines in future. Ultimately, at least common manufacturing processes should become a catalogue item to pick and chose from, to redline it and abbreviated the hours and hours spent to create the same anew.

The Cross Road between Process and Facility

Biopharmaceutical processes converted from large volume, rigid stainless steel designs to small to medium volume, flexible single-use unit operations; from re-usable to single-use. Past facilities, though, were product dedicated and designed to accommodate one product till its lifecycle run out. Afterwards, the facility was mothballed or had to be broken apart to be totally redesigned. This capital intensive way of doing business, is now being challenged by new, innovative ways to design and construct facilities, which will be used for multiple product lifecycles or even multi-product purposes. Facilities are now moving from being single-use to being re-usable. Therefore, processes and facilities cross each others path to the different utilization modus. An often erroneous statement is made about a flexible facility describing a single-use process. Facilities and processes are distinctly different, are designed and constructed in different ways. A facility is not necessarily flexible just because the process is single-use. The opposite is often the fact, traditional facility layouts void the flexibility of single-use processes, since these process are often mobile. If the layout of the facility does not allow easy access or movement, benefits of flexible process equipment is obstructed. To overcome the often stated facility constraints, not just processes require to be flexible, but moreover the facility, meaning the cleanroom infrastructures. Cleanroom spaces, as is, are in place built, ductwork interconnected inflexible room arrangements. The arrangements are dedicated to the product produced and if a new product or process is tried

to implemented in that layout it often causes problems and seen as a facility restriction. New modular facility designs, make it possible to change the layout more rapidly, rebalancing and requalification still being required after the change. The next generation of cleanroom systems and layouts, will not be interconnected, but designed as autonomous units. Any changes in the cleanroom layout, for example an area extension can be done without interrupting current processes. The cleanroom unit would be docked against the existing structure, but not interconnected to a centralized HAVC system. This would mean the facility restriction would be converted to facility flexibility. A linear line-up of the cleanroom units, possibly supported by larger, ballroom type, cleanroom areas would also enable the flexibility of single-use process unit operations. Instead of being blocked in a restrictive design space, flexibility is fully fulfilled for the process and the facility. Ultimately, the requests for flexibility is not just by the industry but regulators alike. The requirement has also been expressed in the FDA's 21st Century Initiative. The vision declares the need for *"A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drugs without extensive regulatory oversight".* This vision may be satisfied with new innovative modular or podular cleanroom systems.

Flexible facilities - What's out there, what's coming ?

For years facilities were complex, lengthy and costly construction projects. The question of when to invest in these, often product dedicated, sites was a prevalent discussion point. To alleviate some of the burden and trying to prequalify a site, container based facilities were introduced. A glimmer of modularity was created, though this type of modularity showed that it still was a complex undertaking to construct such site. Often the promise of ease and flexibility kept unfulfilled, as the assembled systems was as inflexible as the traditional brick and mortar designs. Moreover, the preassembling, disassembling and reassembling of a large amount of container had it is own logistical difficulties and hidden costs attached to it, so much that the initial supply company faltered.

Nowadays, prevalent modular infrastructures are designed with modular panel structures. These systems have a higher flexibility and can be erected fast. If expansions are required, it is easier to take wall panels out and add more area to the overall layout. In most instances, this means that the existing cleanroom areas and processes are interrupted, as the entire cleanroom space need rebalancing. Even so, the modular panel structures have multiple advantages, one of them being of higher quality than the traditional epoxy coated gypsum walls. Wall panel structures can also be introduced into high span shell buildings, instead of the typical concrete or glass structure. This again reduces the capital cost burden and lowers the time to completion, as such shell buildings can be erected in 6-8 weeks, depending on the size. The next generation of cleanroom infrastructures are prefabricated cleanroom units of different sizes and purposes. Instead of having the cleanroom structure build on-site over months with a large quantity of manpower, these systems are build off-site, factory acceptance tested and then shipped to the shell building site. Commonly, the resource loading capacity is limited due to safety and insurance restrictions; therefore, the construction time line can stretch out. Off-site prefabrication avoids these restrictions and the cleanroom units can be installed in days, instead of months. An example for a prefabricated utility module fabrication, showed that 25,000 labor hours were removed from the actual site, which equals 50 workers for 12 weeks. The example showed also better worker safety, since the work was performed on ground level within an environment with

plenty of space and supervision. Another example, showed an on-site labor reduction for prebuilding a cleanroom area by 8,000 hours, a reduction of the labor density on-site by 16 workers for 12 weeks. Added benefit of prefabrication is the lack of need for laydown areas. When stick build or modular cleanroom space is erected, one requires laydown areas for the materials, which can occupy as much as the cleanroom space built.

One might think that these systems are like the old container based designs, but these have multiple distinct differences, one being the size, others the material of construction, also that these do not assemble to an outside total building, but only represent the inside cleanroom structures and require a shell building around them. Most commonly these cleanroom units come also with their own air handler and HVAC system, which means the ductwork is extremely compact, avoiding the typical leakages and pressure losses, therefore reducing unnecessary elevated operating costs. The prefabricated cleanroom units have the benefit that these are build parallel to the shell building, the utilities and process equipment. This often means that the total construction time can be cut in half of what is currently experienced. The first prefabricated manufacturing unit, utilized for an oral solid dosage application, just received the facility of the year (FOYA) award for Equipment Innovation. This facility, with a capacity of 500M tablets, was designed and built in 12 months, which commonly takes 3 or more years. The upfront investment, in this case study, was $15M instead of $40M. In addition, the footprint requirement is reduced by 60 to 70% in comparison to traditional settings and if needed the facility and equipment can be relocated. This facility can be standardized and cloned as multi-platform approach for in country/for country purposes. Another aim is to place these type of prefabricated cleanroom spaces into shell buildings, being either utilized by the same company manufacturing multiple products or by multiple companies using the same quality control, administrative and utility infrastructures. Both options, create faster deployment and capacity scaling, as well as resources efficiencies. Both will lower the typical cost burden, since it is shared and these smaller footprint systems have lower operating costs and/or generate additional revenues due to the faster time to run.

The next step in facility designs will be predesigned facility platforms for different applications, including biologic drug substance and product sites, as well as small volume vaccine manufacturing facilities. This means that the facility layout and design does not have to be reinvented, but in future the end-user scans through a facility platform catalogue and picks and chose the appropriate layout and juts redlines any different layout needs. This will greatly abbreviate the current lengthy design phases, but it also will lower the cost of facilities, by either cloning and standardizing a predesigned site or overall project costs, since it requires less hours to design the site. Conceptual design costs, which are not minimal, could be utilized more efficiently in the basic and detailed design phase. These platform designs are not far fetched, but already exist. Multiple bioproduction platform facilities, drug substance and product, have been designed and delivered, whether as modular wall panel, container based or prefabricated POD based systems. These platforms will extend into other areas, for example work has been done on a 50,000 egg per day vaccine facility, 2,000L monoclonal antibody site, lab infrastructures for analytical and microbial purposes or fill finish unit operations. As single-use process unit operations can be chosen from with a catalogue or electronic platform basis, the same principles should be applicable for facility platforms. This will allow fast and more cost effective project undertakings.

Another, relevant trend are prefabricated cleanroom units including fill lines and their isolators, being drop-shipped to the needed location. This will speed up any capacity increase and could also allow the relocation of such units, if needed. One of the most pressing issues is drug shortage, often worsened by the lack of efficiently running or aging filling systems. This particular problem requires attention and the need to design filling systems, which meet the required quality attributes, but can also be rapidly deployed. Work is in progress for such fill line system and the surrounding isolator and cleanroom environment. Right now small volume, isolator based systems are available within prefabricated cleanroom units. The entire system and structure can be shipped to the location needed and rapidly installed and qualified. Such prefabricated, drop-ship unit operations will need to be expanded to other processing steps. The processes and facilities turn into an easier to chose and build system, becomes very much like a Lego block system. Are we there yet, no, but innovative work is in progress to get there. The facilities of the future, require to be standardized to a certain degree, to be designed, build and qualified faster. Moreover, these facilities will also have the capability to be repurposed and redeployed.

The Cost per Sq.Ft. Thinking; Repeating the Fallacy of Single-use Consumable Costs

Cost pressures have always been high within the industry, though mounting competitive pressures by generics and biosimilars, as well as the call for affordable medicines, make the cost evaluations a priority. However, as it happened with the first cost discussions between stainless steel and single-use processes, the total cost ownership is not taken into consideration, but a tiny snap-shot of the total cost. In the cleanroom area case it restricts itself to the cost per square foot cleanroom space. Not surprisingly, low cost, low quality materials win that race, although these materials have their quality problems and will not suffice over the long run. It is hapless comparison initiative, as much as the consumable cost comparison stainless steel versus single-use. It is nowadays known that the total cost ownership comparison stainless steel versus single-use processes came very much out in favor of single-use technologies. This does not mean that one or the other is the ultimate solution, but all can be a very valuable tool in the toolbox of options. The dismissal of innovative technologies, by glancing over one value attribute is a major fallacy. It will not create efficiency, optimization and modernization, but backwards progress compared to adopters of new technologies. A great summary of the above is the statement by the American physicist William Pollard, "The arrogance of success is to think that what you did yesterday will be sufficient for tomorrow". The statement was recently cited during a presentation of the new Amgen facility in Singapore, a facility, which shows so many benefits in regard to cost savings and higher efficiencies, from an 80% site reduction with the same throughput as a traditional site to a 5-fold reduction of energy consumption. Examples of higher efficiencies, capital and operational cost savings of new and innovative facility design are more and more forthcoming. The costs or economies of the entire systems has to be determined and not a narrow sliver of influencers.
Following table just defines a few of the parameters, which require to be investigated to make the appropriate choice.

Personnel needs	Construction personnel needs at the site, including supervision and security are often underestimated. If the FTE density allowance is reached, timelines can slip. The insurance costs of the construction site require to be taken in account. Prefabricated systems or rapidly build infrastructures will lower the costs

	involved. In addition, once the facility is running the FTE's used to run the site have an influence. Lower volume, but higher efficiency processes and sites require lower FTE level and safe therefore costs.
Design time and costs	Often sites are redesigned instead of utilizing former experiences. If facilities or cleanroom infrastructures could be copied, design timelines and costs are greatly reduced, qualification activities abbreviated and possible problem points are known.
Construction site space	Laydown area may be needed to store construction materials. In instances that space need can be as large as the actual build-out cleanroom space. Off-site prefabrication can reduce the space needs to assemble the infrastructure within the building.
Superstructure and mezzanine levels	Traditional sites require large mezzanine areas to run miles of ductwork. This is space, which needs to be added into the cost calculation. Possible compact and decentralized air distribution systems could reduce the space needs. In addition, the more compact the ductwork, the lower the possibilities of pressure losses and therefore higher energy consumption.
Material choices	Hidden are the costs of bad quality and cheap choices have the inherent risk of not meeting the required quality standards or long-term needs. New materials being introduced have not just the required quality longevity, but also reduce possible secondary contamination risks, like mold.
Scalability	In instances of the need of additional manufacturing space, interconnected cleanroom infrastructures will be disrupted by opening the existing infrastructure. Future manufacturing needs require to be investigated as early as possible to determine whether scaling without interrupting existing process is possible. The costs of production interruptions require to be accounted for when making facility design choices.
Time-to-run	How fast can the facility be deployed is a critical economic parameter. Any day lost in manufacturing, attributes to losses in revenue. Therefore, facility designs cannot just be judged by costs, but also require an appropriate net present value analysis.
Depreciation	Depending on the facility structure the depreciation of the asset can be different. If the cleanroom space can be classified as equipment, the depreciation can happen in 5-7 years, in comparison to the typical 20-30 years.
Sanitization	It may not be considered a major factor how easy a facility or cleanroom infrastructure can be sanitized, but past contamination occurrences showed a major impact due to business interruptions. In one instances, the contamination could not be easily traced, which resulted that the entire building was fumigated, causing a 6 months production interruption. Such potential disruption may be avoided with appropriate segregation and containment, which can be sanitized using for example vaporized hydrogen peroxide.
Repurposability	The other impact is the repurposability of a production area. When the facility or production area is product dedicated, it will be used for the product lifecycle only, which can be seen as

	inefficient. This means that upfront design choices require to take such sunk cost considerations into account. If there is a possibility to repurpose the area, when the product lifecycle ends, the efficiencies become obvious.

It is obvious, that the list of costs is not exhausted by just checking the cost per square foot. In addition to making the right choices of the infrastructure design needs, a multitude of critical cost items need to be investigated in detail to determine, which solution is the most economic and efficient. The same tunnel view may be applied as it happened with single-use process technologies, only one factor is checked and elevated to the highest priority, instead of the totality of cost factors. It may be driven to that single point evaluation extreme by entities who desire man-hour accumulation. This though may not be what is best for the industry and the cost per dose. We require to shift to different evaluation models and design systems to speed up time-to-run and lower the costs.

Conclusion

Facility design requirements are shifting. The bioprocess technologies have encountered the transformation from stainless steel to flexible and agile single-use process technologies. These innovative technologies created new opportunities, not just in process designs, but also interconnecting process, making processes more efficient. Similar claims cannot be made for the facility part. When discussions arise about flexible facilities, often single-use technology is mentioned, however that is not the facility but the process. This shows that the mind-set of change to total flexibility stopped short and often flexible processes are still forced into uncompromising, inflexible facility and cleanroom infrastructures. Total flexibility means the fusion of flexible processes with flexible facilities. The designs require to fit specific applications and therefore require flexibilities, which have not been experienced in the past. With such flexibility demands, the infrastructures, building materials and construction mode changes. Outside the box thinking instead of holding steadfast to the same and traditional is needed. As process technologies have an assortment of choices or tools in the toolbox, to design the optimal process stream, so do facility constructions and designs convert to an increasing selection of known and new, innovative tools.

Flexible facility platforms are becoming or are available. The future of facilities requires to be modularity, either as panel or prefabricated systems, progressing to potentially clonable platform designs. The customary hesitancy though is as prevalent as it was with single-use technologies. The total cost comparison is needed to convince, as it was necessary for single-use technologies. The costs of consumables were compared to re-usable process equipment and seen as too expensive. This changed with evaluations, which showed that not just the lower costs, the increased capacity utilization, but also reduced carbon footprint were published and showed the complete benefit picture of single-use technologies. Once the total cost ownership of single-use versus re-usable process technologies were established and compared, single-use processes were adopted rapidly. New facility designs and cleanroom structures experience the same fallacy as single-use technology in the beginning of its days. Instead of evaluating the total cost ownership the comparison restricts itself to cost per square foot, which often is only taking the cleanroom space into account, not even the mechanical or automation needs. With that incomplete mind-set, true opportunities stay unevaluated and the call for flexibility limited to the processes. Once the

mind-set changes due to the experiences of the early adopters, single-use processes and facility platforms will become the optimal flexible solution and will compliment each other. Stretching the imagination, one can see additional opportunities by creating facility platform designs, which will be listed within a catalogue format and chosen as process equipment. The platforms could be redlined and modified, but overall lengthy design times are reduced greatly with a platform approach. This platform approach can be segregated as unit operation, which then can be combined to an entire process respectively facility. Ultimately, the request for flexible facilities, the search for the facility of the future, will move the traditional though process to a necessary paradigm shift of evaluating the new, unknown and innovative.

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