The Call for Agile, Flexible Facilities

How podular facilities may answer it

By Maik W. Jornitz, COO G-CON Manufacturing Inc.

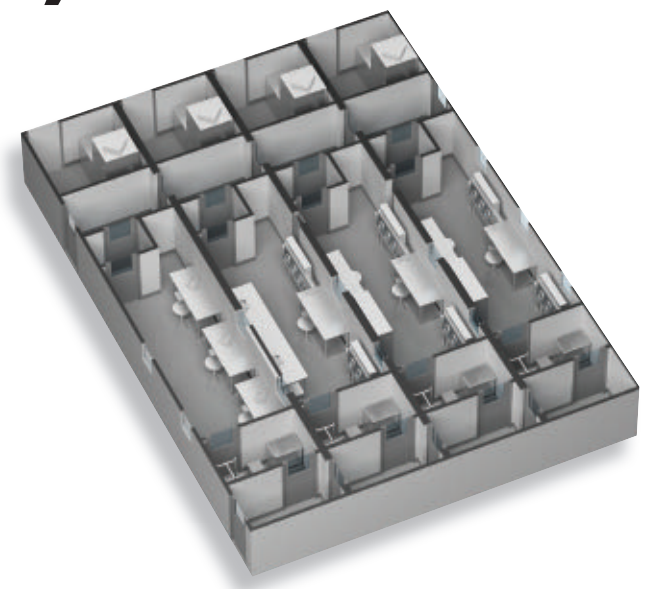

Figure 1: Podular cleanroom structure with independent air handling system

The call for agile, flexible facilities, which deliver high quality medicinal drug products is not new [1, 2, 3] and the FDA's 21st Century Initiative vision added emphasis. The vision declares the need for *"A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drugs without extensive regulatory oversight"*. Once again, it is not new, but it has sprung up multiple times over the last few months and the focus on agile and flexible facilities has increased significantly, due to an ever increasing need for smaller volume, multi-product manufacturing. In addition, facilities are getting older and require improvements, some of which have been linked to drug shortages.

Agile and flexible facilities are now being publicized as readily available. However, the word facilities is often mixed-up with processes and single-use process technology being introduced as flexible facilities. Processes and facility designs are interlinked, though should not be mixed up. A single-use technology process is not necessarily a flexible facility.

Furthermore, modular facility designs, either as wall paneled system, container based or prefabricated stick-build systems are often promoted as flexible [4]. The question one requires to post, what does flexible mean? Faster build-up of the cleanroom infrastructure? That would probably only justify a lesser portion of the real meaning of flexibility [5, 6].

The paper disseminates how agile and flexible facilities may be defined and how these facilities can be achieved.

FLEXIBILITY AND SINGLE-USE TECHNOLOGY

It is well understood that single-use technologies can make process and unit operations more flexible [7, 8]. The typical rigidity of hard piped, stainless steel laden processes, with its lengthy turnover times is removed and replaced with disposable process equipment. That disposability not only allows faster turnaround to re-use the process, due to avoiding lengthy cleaning and steaming cycles, but also creates the possibility to use the same production space for different products. The introduction of single-use unit operations augmented that concept, as these closed systems could be connected to each other without breaching the aseptic barrier. Single-use process systems create processing flexibility as the volumes processed can be changed due to the different single-use configurations and potentially multi-products can be processed, since the processing equipment is not re-used, but discarded after use. The benefits have been pointed out in multiple publications, not just being technology, but also economical benefits.

Having said this, in instances single-use technology and the reiteration of being a closed system may create overconfidence, so much that calls for lower classification cleanroom or ballroom design cleanrooms space are voiced. It goes so far that a statement was made; "one can run such single-use closed process within a garage environment". Questions arise, why hard piped stainless steel systems cannot be classified as closed and what happens when there is a leak in one of the single-use components. It would be advisable to perform a risk assessment before one rushes into the supposed cost savings of lower cleanroom classification and lesser personnel needs, as one batch loss or production stop may eradicate all the savings and more. The argument of integrity testing of single-use equipment will prevent such adverse events may be extended, however the integrity tests evaluated so far are merely quantitative and may not determine minute material weaknesses.

Moreover, process flexibility should not be mixed up with facility flexibility. Yes single-use technology may promote a ballroom or lower cleanroom classification approach, though that does not make a facility agile and flexible, but just supports a part of the need.

AGILITY AND FLEXIBILITY

One can dive into the dictionary to find the definitions of these two terms, but for the biopharmaceutical industry these terms mean:

- Capacity scalability (up and down)
- Multi-product production
- Short time-to-run or rapid deployment
- Rapid change-over or changes in the layout
- Repurposability
- Mobility

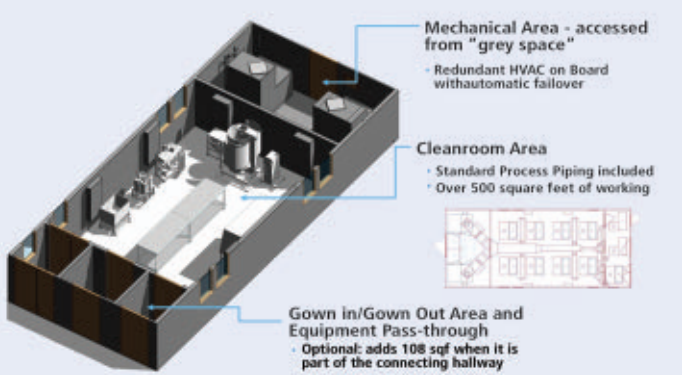

Figure 2: Podular cleanroom with integrated access and exit corridor system

The latter two are new and unique features, which are being asked for. The industry does not want to mothball assets any longer, but repurpose such assets after the product lifecycle for the manufactured product ended. In addition, when a cleanroom asset can be repurposed it becomes a lower investment risk also for start-up companies. Mobility is required due to the need for relocation. That pursuit will not happen too often, but the feasibility of moving assets is embraced since such assets can be rapidly deployed in regions of needs.

The focus though of agility and flexibility lies within the scalability of production assets and the multi-product processing opportunity. Both will support the reduction of the cost of goods sold, since the capacity utilization will be adjusted to an optimum. The process can be scaled up or down, which mean the process and facility grows or shrinks with the demand or volume change. In addition, the combination of single-use technology and sanitizable, autonomous containment options, like podular systems, support the multi-product manufacturing possibility. This new combination of process and facility flexibility represents a quantum leap from the known traditional brick and mortar sites. It also inherits real flexibility and not perceived flexibility as with modular systems, which, when assembled, just represent the traditional set-up.

PODULAR FACILITIES MEETING THE CRITERIA

Multiple facility options have been introduced and tried, most of them did ultimately end up as a product dedicated, fixed installation without the possibility to be repurposed, but being either mothballed or finally being subjected to the wrecking ball. For example modular solutions look very flexible from the standpoint of initial design and build, but once installed any changes to a centralized air handling, interlinked cleanroom system become a major re-qualification task, not to mention that the substantial duct work is difficult to sanitize. It may be so, that the capital investment is lower than other alternatives, but such financial review does not take into account the operating costs, influenced by leaks and temperature gradients within the superstructure. Or the lack of repurposing such infrastructure, meaning the lifespan is very limited.

Nevertheless, the financials are not the focus of this paper, but the lack of true flexibility. Scalability and multi-product manufacture, the two major prerequisites of agility and flexibility are at least foiled by the interdependence of the cleanroom/air-handling infrastructure [9]. To achieve cleanroom infrastructures respectively facility agility and flexibility, one has to look at separating the unit operations, similar to the process. Cleanroom areas require being autonomous, independent and not interconnected by ductwork. The ductwork itself shall be compact, miniaturized to be sanitized with ease, to avoid leaks, pressure loss and temperature changes. The cleanroom system needs to be a mobile independent system, which either serves unit operations or an entire process.

Such systems can be found as podular structures or autonomous cleanroom PODs (Fig. 1.). These are not container based, once again interconnected systems, but differ greatly due to the air handling system in every one of the PODs, which create autonomy. Podular systems can be moved into a shell building, owned or leased, and either be accessible via a corridor system or include the corridor system within the podular structure (Fig. 2.). These cleanroom systems become more and more widespread, since the time-to-run is greatly reduced, as these cleanrooms are built off-site within weeks, can be moved with ease via air bearings and are repurposable. In addition, the need for sanitization of the cleanroom space and the compact ductwork is satisfied with vaporized hydrogen peroxide. These structures represent agility and flexibility in all respects listed above and are another facility infrastructure option. After the leap from inflexible stainless steel processing structures to flexible single-use technology, facilities undergo the same leap and ultimately will end up in the flexibility corner [10]. ■

REFERENCES

1. A. Shanley, P. Thomas (2009), "Flexible Pharma: Puzzling Out the Plant of the Future", PharmaManufacturing.com
2. P. Thomas (2012), "Biopharma's Future Facilities: Smaller Footprints, Complexities, and Costs", PharmaManufacturing.com
3. H.L. Levine, J.E. Lilja, R. Stock, H. Hummel, S.D. Jones (2012), "Efficient, Flexible Facilities for the 21st Century", Bioprocess International
4. P. Almhem (2013) "Modular/Flexible Facilities", Pharmaceutical Processing
5. A. Pralong (2013) "Single-use technologies and facility layout – a paradigm shift", Biopharma Asia Magazine, Vol 2, Issue 1
6. M.W. Jornitz (2013) "Defining Flexible Facilities: When is a flexible facility being flexible?", Pharmaceutical Processing
7. A. Sinclair and M. Monge (2002) "Quantitative Economic Evaluation of Single Use Disposables in Bioprocessing", Pharmaceutical Engineering
8. P.M. Priebe (2004) "Advances in Fluid Processing Technologies", PDA SciTech Conference
9. F. Nowbakh (2004) "HVAC Design for Multi-Product Manufacturing", Controlled Environments Magazine
10. M.W. Jornitz (2014) "Podified Manufacturing Facilities and Risk Mitigation of Aging Pharmaceutical Facilities", Pharmaceutical Online