International Journal of Pharmaceutical Science Invention
ISSN (Online): 2319 – 6718, ISSN (Print): 2319 – 670X
www.ijpsi.org Volume 6 Issue 2 ǁ February 2017 ǁ PP. 26-30

Analyzing the Flexibility of Pharmaceutical and Biopharmaceutical Facility Options

Sidney Backstrom,
Executive Director, Business Management, G-CON Manufacturing, Inc.

I. Introduction

In the pharmaceutical and biopharmaceutical industry several factors have converged to change the landscape in regard to facilities: the wide scale adoption of single use equipment, greater emphasis on reducing capital expenditures, the need for "in country for country" production, and the advent of personalized medicines and industry focus on orphan drug production to name a few. Such factors militate against the traditional brick and mortar facility approach which is designed for the forecasted global production demand of a blockbuster quantity of product. The expense to build and operate, time to build and validate, single-use nature, and risk of product loss based on building a facility based on forecasted demand,have caused the Goliaths and Davids of the industry to seek a better solution. The search for that solution will inevitably lead the tasked construction project manager to a single word that is often incanted in the facilities world – flexibility. he or she will look for it or be told that he or she needs it in the chosen option.

What does this profound incantation mean you ask?One can look high and low in white papers, presentations, articles and the like but at least with respect to the pharma and biopharma industry there does not seem to be a settled upon definition.[1] So let's begin at the beginning. What is the definition of flexibility? Merriam-Webster defines flexible or flexibility as "characterized by a ready capability to adapt to new, different, or changing requirements." Applying that definition to pharma and/or biopharma production, what does that mean? Substituting in the subject we are concerned with, the facility has to be readily capable to adapt to new, different or changing requirements. In the pharma and biotech context new, different or changing requirements seem most closely related to:

- capacity, either more or less than originally contemplated;
- a change in process;
- change in regulatory requirements;
- the need to move the production capability, due to shifting demand needs or political instability;
- the need add a new product or replace an existing product; and/or
- the need to respond to an excursion or contamination issue.

The question is, do any of the current facility schemes allow for this flexibility? To answer the question we must consider what the current facility options are.Theoptions readily available today are: modular construction onsite, modular construction off-site, stick-built construction and/or pre-fabricated cleanroom modules. Defining each further is in order.

Modular construction onsite is generally considered as building processing space using modular panels at the ultimate production location. There are many companies that provide such panels. Some even provide for the installation of the panels. There are many cleanroom contractors who can assemble such panels onsite.

Modular construction offsite is generally considered to be building an entire facility at a manufacturing location module by module, then erecting a structure entirely of those modules and

[1]See, for example, H. L. Levine, J. E. Lilja, R. Stock, H. Hummel, S. D. Jones (2012) Efficient, Flexible Facilities for the 21st Century, BioProcess International 10(11); Hodge G. Hodge (2009) The Economic and Strategic Value of Flexible Manufacturing Capacity. *ISPE Strasbourg Conference,* 28–29 September 2009, Strasbourg, France; A. Shanley, P. Thomas (2009) Flexible Pharma: Puzzling Out the Plant of the Future, PharmaManufacturing.com

connecting the modules, testing the facility for functionality and then disassembling the facility, shipping the modules individually and re-erecting the facility with the modules at the ultimate production site.

Stick built construction is commonly regarded as building internal infrastructures, cleanrooms and ancillary spaces, at the production site. Gypsum wall board is generally used if panels are not.

Pre-fabricated cleanrooms are offsite built modules that provide clean space including floors, walls, ceilings, windows and doors in appropriate finishes. In some instances such modules include their own mechanical space where automation PLCs, HVAC, fire suppression systems, utility connections, etc.are housed.

Analysis of the Options – Flexible or Not

Modular construction onsite. Using panel systems, it is not hard to appreciate that there is some flexibility benefit. In a greenfield or brownfield application, the cleanroom build out can morph to the layout of the host facility. If the host facility is a large rectangular clear span facility, the cleanrooms can be built in a large rectangular arrangement. If the host facility is partially built out and has columns in the unimproved area, the panelized approach can be contained in that space. The approach can be likened to making "houses" out of playing cards. There is no inherent limit to the size and shape.

But is this apparent flexibility valuable? In deciding that, it should be noted that every other option mentioned above has the same flexibility. Each, whether it is stick built or offsite modular, can be sized according to the client's desires. So this apparent flexibility really has no relative value.[2]

A more important analysis would be to consider whether modular construction onsite can meet the new, different or changing requirements identified above. That analysis is below:

- Change in capacity – modular construction onsite, while initially flexible in terms of size and shape, is not very malleable once it is built. Wall panels, doors, ceilings and the like are permanently placed in position. Ductwork and utilities are provided in intricate detail above the cleanroom structures. Adding to or reducing the footprint of the fixed structures requires onsite construction or demolition, which will interrupt ongoing production. Once construction and/or demolition are complete, rebalancing of the HVAC system and revalidation of the cleanroom space will be required.
- Change in process – would lead to a similar result if the change in process required more or less space, different air classification, or a different flow of materials, waste or personnel. All of these changes would require some form of construction onsite which would interrupt ongoing operations and require re-validation of the cleanroom space.
- Change in regulatory requirements – whether it be air classification, pressurization, flows, washing, gowning, etc. - one can scarcely imagine a scenario that doesn't affect the HVAC, utilities requirements, and/or footprint of the cleanroom space. And any of those changes would require onsite construction or changes to mechanical equipment, such that production is interrupted and revalidation required after changes are made.
- Adding a new product or changing product being produced – a critical step in such an endeavor is cleaning the cleanroom and ductwork. While the cleanroom itself may be able to be cleaned, the extensive ductwork above ceiling may present a formidable challenge. Moreover, unless the new product requires the same footprint, processing equipment, process flows, etc., it is very easy to see that some amount of retro-fitting will be required leading again to interruptions and revalidation efforts.
- Contamination –if an excursion occurs or contamination is discovered, it is likely that decontaminating the entire cleanroom area will be required as it is most common that all of the cleanroom spaces will share HVAC equipment and airflow. In that instance, cleaning in the area of the spill or contamination only will not sufficiently clean the affected area. The entire area will have to be cleaned resulting in downtime and revalidation once the system is brought back up.

[2] A simple example illustrates the point. If everyone in the country is given $100, has anyone gained any wealth?

- Moving production capacity – if there is a desire to move production from one facility to the next or even from city or country to another, it is universally accepted that deconstructing the panels, moving then and reconstructing them would not be feasible or time efficient.

Modular construction offsite. This approach has been employed by a number of entities, some still operating and some not. While the concept has visceral appeal, in practice there are shortcomings. On the appealing side, being able to build offsite ostensibly provides the ability to build without permitting delays and without the need for the client to oversee the construction onsite. Permitting though is not foregone but only delayed as permitting for the construction onsite will still be required. Construction oversight will also be required offsite at the manufacturing site and then again upon delivery. So these two benefits are really just extending the time before such activity is required.See Figure 1, (below) courtesy of Jacobs.

How does modular construction offsite fare as it relates to new, different or changing requirements? Let's consider the points previously considered:

- Change in capacity – The modular building has been designed, built, disassembled, shipped and rebuilt onsite. The modules have been permanently connected to one another as have the utilities and HVAC throughout the facility. Increasing the capacity would require more or larger processing equipment which would also increase the space needed as well as utility and heat loads. Adding to meet these requirements in a now hardened facility is not feasible. The additional capacity would require either a new facility or "bolt on" approach similar to adding a tool shed in the backyard when the garage gets full. Reducing the capacity would simply means less of the hardened facility is used. Redeploying that space is not possible.
- Change in process – recalling the examples previously considered, or adding a step or taking away a step, would all result in some construction or re-balancing onsite or losing the efficacy of some previously used space.
- Change in regulatory requirements –reviewing the examples noted above, e.g., change in product, personnel or waste flow, none of them can be readily accomplished without some modification to the overall process flow or mechanical plan of the building.
- Adding a product or changing products – Adding a product and not affecting the production capacity of the original product cannot be accomplished unless the building was originally designed with this excess capacity in mind. Such would not be a tribute to the flexibility of the facility. Credit in that case would be due to planning and a much higher budget. Changing products would require a complete facility sanitization and validation of the new process. Such could be accomplished but time and costs loom large in such an effort. The number of mothballed pharma facilities stands as a testament to the unenticing nature of this decision.
- Contamination – given that centralized HVAC systems are employed in this type of construction in the same way that they are in brick and mortar facilities, a contamination in one area is likely to spread to others. There have been many examples of facility contamination and the efforts taken to remedy it. The process halts production, is time consuming and expensive. The hardened nature of this type of facility would lead to no different result.
- Moving production capacity – not cost or time efficient.

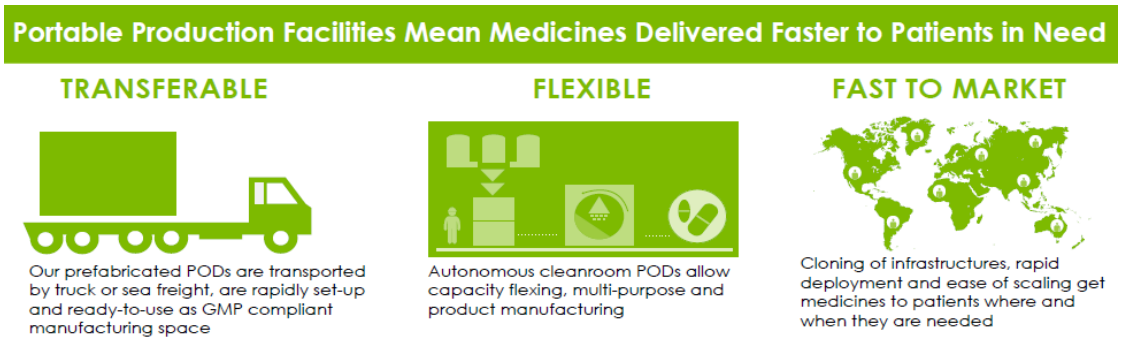
Stick built.This method is probably the best known option for the life sciences industry. Building cleanrooms in place within a facility is well understood both in terms of its benefits and shortcomings. It is similar to the modular construction onsite in terms of being construction onsite, requiring permits, initial flexibility of design, etc. But it is

even less flexible than the paneled approach. In the paneled approach, walls can be moved more easily than a stick built wall which is most often gypsum board covered with epoxy. Moving a wall in this option means demolition. Both suffer in regard to changes in utilities or HVAC distribution. Centralized distribution of both requires adding capacity and rebalancing with respect to HVAC. Assessing this methodology against the six categories of change, it fares slightly worse than the modular construction onsite scoring the same on four areas (change in capacity, process and regulatory and ability to move) and about the same on two (product change and contamination).

Pre-fabricated cleanrooms. The relatively new kid on the block, pre-fabricated cleanrooms emerged onto the scene almost ten years ago. These cleanrooms are built offsite, tested, shipped and then put in place in the production facility. See Figure 2, (below) courtesy of G-CON Manufacturing, Inc. The most advanced form includes their own HVAC systems within the cleanroom footprint providing compactness and autonomy from the facility or other cleanrooms. Such a characteristic is a major distinguishing factor in regard to other options and has been recognized by leaders in the industry as a major advantage.[3] They can function alone or as part of a cleanroom cluster where larger processes can be accommodated.[4]

An analysis of the five points considered for this option is required.

- Change in capacity – While it may seem that changes in capacity would not be possible with such discrete units, the contrary is true. New units can be added when needed and without interrupting the existing process. They can be added in a linear fashion or added to the existing cluster via the use of a corridor or previously placed knock out panel. A reduction in capacity in this context does not mean that previously placed units are shut down. Rather, they can be disconnected and moved out of the facility for deployment elsewhere.See Figure 3, below, Courtesy of Pfizer.



[3]A. Pralong (2013) Single-use technologies and facility layout – a paradigm shift, Biopharma Asia Magazine, Vol 2, Issue 1 ("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.")

[4]P. Nixon, (2015) Transforming the Pharmaceutical Industry: Portable, Continuous, Miniature & Modular Development and Manufacturing (PCMM),2015 PDA/FDA Joint Regulatory Conference. (explaining the benefits of per-fabricated cleanrooms in an oral solid dosage application)

- Change in process. If steps are added or taken away, air classification changes, etc. units can be added or reduced. Additional capacity from each internal air handler can be deployed. Importantly, the use of individual air handlers per unit or unit cluster allows for changes to air flow, air changes per hour, etc. without having to add to or rebalance the entire system.
- Regulatory changes – Much like the way a change in process can be accommodated, a regulatory change can also be accommodated. Units can be added or taken away like "Legos" within the larger open warehouse type structure that houses the units.
- Adding or changing a product – with the ability to have discrete process steps in each unit adding a new product line into a facility simply requires adding additional units to accommodate the process. Changing the product means complete sanitization of the units, which given their integrated HVAC system, is significantly less challenging than cleaning elaborate facility wide ductwork.
- Contamination – because of the separate HVAC of the units and unit clusters, contamination can be well-contained and if necessary the affected units can be removed from service and replaced with other units or returned after decontamination if such was completed offsite.[5]
- Moving – This is the only option that can be effectively moved either within the facility or out of a facility. If demand lags in a particular area, the entire production process can be picked up and moved to where the demand is.

So What Have We Learned?

Having reviewed the leading facility options and seeking to determine if flexibility is a characteristic of each, we have learned about each offering. We have learned that all offer initial flexibility, i.e., the ability to design what is desired. But this flexibility is no different from the flexibility offered by a traditional brick and mortar building. And this flexibility is really not valuable relative to other options because all options offer it. Some options offer additional flexibility, the ability to morph into a space already built – onsite modular, stick built and pre-fabricated cleanrooms. But only one proves to offer flexibility beyond that – flexibility once the system has been built and placed. Prefabricated autonomous cleanrooms stand well above the rest in terms of their ability to meet the true definition of flexibility, the ability to meet new, different or changing requirements. So if true flexibility is desired, autonomous pre-fabricated cleanrooms stand well above the rest.

[5] At least one provider of this technology uses integrated air-bearings within each unit that allows the unit to float like an air hockey puck over a flat concrete surface. Such makes the need for indoor lifting unnecessary and allows for easy moving into and out of the facility.