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Flexible Facilities Roundtable

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Have you seen a growth in the demand for flexible/ portable equipment?

Dr. Katherine A. Bakeev: There has been a growth in the availability of portable instrumentation, which has been driven by demand over the past decade or more, and the concomitant advances in optics, electronics and supporting technologies that make this possible. The demand for the flexibility and portability of instrumentation is related to the needs and also desire to make measurements in different environments without needing to always transport samples back to a central laboratory location. Even consumers have increasing desire to have capabilities to measure products for quality before purchase, which portable instrumentation makes possible.

Maik W. Jornitz: Yes, as the biopharmaceutical industry is converting from large scale, large volume production systems, the adoption of flexible single-use equipment became more prevalent. However, single-use equipment flexibility is only as good as the cleanroom infrastructure around it. Therefore, the majority of the drug manufacturing industry searches for and adopts flexible facility designs, like prefabricated cleanroom PODs, which work synergistically with flexible single-use processes. Moreover, new, innovative facility designs allow shortening the time-to-run greatly, and create the possibilities for multi-purpose/ multi-product processing and repurposing of such infrastructure.

Rob Noel, PhD: The demand for flexible/modular equipment is unrelenting for the production of clinical trial materials. Flexible manufacturing equipment also extends to commercial, approved therapeutics, particularly if the manufacturing demand is sporadic or not easy to predict.

Surendra Balekai: There has been significant demand from various segments of the industry for modular equipment. Most of the biological industry is working on innovative and others on biosimilar molecules. Each one has a pipeline of 2 – 20 molecules at various different stages and most of these molecules are in clinical phases. This triggers need for flexible/modular facilities to accommodate multiple products.

What types of processes are best suited for flexible/portable equipment?

Bakeev: One of the benefits of portable equipment is that it can be used with many processes, without having to be dedicated and permanently installed in a single process. For analytical instruments such as portable Raman, the portable instrumentation provides the ability to use it during process development and use it in whichever lab, vessel, and pilot plant that it is needed. Handheld instrumentation can reduce the necessity of transporting samples to a laboratory for analysis, which is especially useful when the rapid identification of incoming raw material is needed. Measurements can be made at the point of material receipt, with material in their original containers.

Jornitz: Initially we thought flexible cleanroom PODs would mainly be used for bioprocessing purposes, but as it turns out the array of manufacturing applications is by far broader. We can now implement continuous oral solid dosage form processing into prefabricated cleanroom units; fill/finish systems, which potentially can be drop-shipped with the equipment integrated; and cell therapy applications, which require robust containment and the possibility to sanitize entire cleanroom units with vaporized hydrogen peroxide. Requests for new facility designs range from 2,000 L antibody POD platforms, to smaller scale egg-based vaccine facilities, to transmissible disease containment units and patient care systems. This does not mean that these prefabricated, autonomous cleanroom systems are a fit-for-all, but these certainly serve a wide field of applications.

Noel: Therapeutics with smaller patient populations or/and with higher potency (lower dose quantities) do not tend to need dedicated manufacturing facilities and therefore are best produced in flexible facilities with flexible processes and equipment.

Balekai: Until 3 years ago adoption of flexible/portable equipment was limited to bioreactors, some mixing applications like media/ buffer prep and intermediate storage applications. In the last 3 years there has been significant expansion of flexible/portable equipment for downstream applications like virus inactivation, final drug formulation, final bulk storage applications, freeze/thaw, frozen shipping etc. In short, excluding centrifugation, ultrafiltration and chromatography most of the unit operations are now preferred in flexible/portable format.

In addition to cost savings and processing efficiencies are there any other significant benefits inherent to flexible facilities/equipment?

Bakeev: Flexible, portable equipment increase the analytical capabilities throughout a plant, as the instrumentation can be taken where it is needed, and is often designed with an intuitive user interface that can be used by non-expert users as well as expert users. This added capability contributes to greater product quality, and time savings as samples can be measured wherever they are. This provides more timely results, reduces the need for sampling and sample transport, and can also reduce the number of people involved in providing information to verify incoming materials,

measure a process, confirm the completion of a production process, etc.

Jornitz: There are a multitude of advantages, which were untapped before these flexible units, PODs, were introduced. In comparison to traditional and modular facility designs; prefabricated, autonomous cleanroom units can be deployed by far more rapidly, are pre-qualified before they leave the production site, can be repurposed and relocated, if needed, are robustly sanitizable with vaporized hydrogen peroxide, have a lifespan of 25-30 years, can be depreciated as equipment, are scalable without interrupting existing production areas, can be truly cloned without material or contractor variation, do not require laydown area, neither a large swath of personnel at the construction site, can be built parallel to the shell building and process equipment. These are only a few of the advantages. It does not mean that these systems are a “silver bullet”, but definitely can be an alternative to existing offerings or implemented as a hybrid solution.

Noel: Downstream process operations from one therapeutic to another can be quite different in functionality and relative position in the process; flexible as opposed to fixed position unit operations becomes even more important in these instances.

Balekai: Flexible facilities enable molecules to get to market faster, reduce contamination risks/losses and the massive amount of documentation that is required especially in product change over.

Are there any regulatory requirements that are unique to flexible facilities?

Bakeev: Flexible equipment and facilities are subject to the same regulatory rigor as the other equipment and facilities used. Consideration needs to be made for qualifying the items in a typical environment where it will be used which may include consideration of battery and other backup power needs.

Jornitz: No, these flexible cleanroom units represent the most robust containment system, since these units are not interconnected with each other, but are autonomous. This means any excursion can be addressed by location and does not need to affect the entire site. Regulators see the adoption of new technologies as beneficial to truly gain the benefits of Quality by Design initiatives and FDA’s 21st Century Initiative vision. The vision declares the need for “A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drugs without extensive regulatory oversight”.

Noel: The same manufacturing principles and regulations are used for both flexible or fixed facilities; batch to batch cross contamination or product to product crossover are both important to avoid. As with any new technology or procedure introduced into a regulated environment, a greater amount of internal and external scrutiny is required.

Balekai: There are guidelines from BPSA and BPOG. There are no standard regulatory requirements unique to flexible facilities. However, industry is expected to comply with regulatory needs from the product and process perspective.

What do you see for the future of flexible equipment/facilities?

Bakeev: The adoption of flexible and portable equipment will continue to grow so that companies can acquire assets that can be used as broadly as possible to meet their needs. As instrumentation miniaturization develops further, the advantages this brings in the ability to measure starting materials and products more easily, more frequently and with less movement of materials will result in higher assurance of product quality. This flexibility and increased testing ability

will help to identify potential issues earlier, thus resulting in higher product quality reaching final customers.

Jornitz: For decades we discussed the need for flexibility, for efficiency and rapid technology adoption, but so far we have stopped short to "walk the talk." Today we see such adoptions happening due to the need to stay innovative, but also competitive. Competitive not only means lower costs, but rather optimal capacity utilization by being able to flex capacities up and down, upon demand, without creating a tremendous operating and overhead expense. It also means incountry/ for country manufacturing sites to avoid elevated cold chain costs and import duties. It means to be able to produce a development, clinical material and production scale batch within the same process. It also means production process designs and facilities are required to be repurposable and not become another mothballed monument. These few examples show that the majority of future production processes and sites will need to be flexible and agile to be able to supply affordable medicinal drug products to a larger patient base.

Noel: There are lots of factors that will dictate the future demand for flexible facilities and equipment. The reliability, automation, integration, consumables standardization, support and ease of use of the equipment itself will be key; helping to drive the adoption of a greater number of smaller facilities responding to regional demands.

Balekai: As of today, industry is under pressure to build facilities for multi products and have flexibility for capacities. Moving forward this will be standard. Molecules in the clinical phase need a couple of batches processed. Flexible equipment/facilities are the most economical way to build, manage and sustain. Millions of dollars are spent in maintenance of traditional facilities, industry can’t afford to and doesn't want to continue down this path.

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