Production Progress

Biopharma production facilities are evolving: smaller, simpler designs are faster to implement and update, leading to lower costs. While there is a certain amount of resistance to such modern concepts, there is clearly a demand for a new approach

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A revolution in biopharmaceutical production facilities design is not to be expected. Instead, companies should look to a more continuous evolution through trial and error. The engineering pipeline is full of untested ideas and concepts that need to be proven and, more importantly, accepted by the industry and regulatory bodies. But clear business needs like cost reduction, new markets and global presence are the driving forces behind a reshape of biopharma production and, consequently, facility design.

Evolving Vision

Flexibility is the word that best describes the ultimate vision. An adaptable facility should be one that is available whenever needed; is deployed at the most convenient location; will secure market supply and adapt to product demand; will allow the setting-up of any production processes and continue to operate at the highest efficiency; and, of course, is compliant with Good Manufacturing Practice (GMP) principles. It should also respond to today's sustainability and environmental requirements.

Facilities have always been flexible – multi-purpose, for example – but have, until recently, followed a different approach: designed and built with long-term utilisation in mind. However, in the modern business world, 'long-term' is reduced to just a few years, characterised by fast, continuous changes and uncertainties. Now, to adapt to this new environment, facilities must be more agile and responsive.

The list of technology elements that contribute towards increased flexibility is long (see Figure 1, page 20). It encompasses product demand to new GMP approaches, through to continuous processing and the deployment of manufacturing excellence principles on the production floor – each element representing a potential change. However, independently, these adjustments may not be as powerful as when they are combined.

Efficient Processes

In the past, the pharmaceutical industry – being regulated and protected from strong competition – had accepted the necessity of basing production on processes that would remain unchanged throughout their entire lifecycle, regardless of their weaknesses; reproducibility was identified as the essential element to preserving product quality and safety.

Now, with increasing competition and price pressure, there is a need to introduce efficiency tools to enhance new approaches throughout the entire product lifecycle. These can begin with the submission of a new application following Quality by Design (QbD) principles – design space concepts, for example – that could later translate into a different product control strategy, approval of process changes, or the criteria applied for product release.

A risk-based approach should open the door to new methods or solutions, as long as it can demonstrate that the process will not bring additional risk to the product and, ultimately, the patient. For instance, it should be possible to challenge cleanroom classification or area segregation on the production floor.

It is expected that production excellence principles, focused on the added value stream, can alter production organisation to minimise waste – also referred to as 'muda' – within a manufacturing process, such as stocks of raw materials, buffer and media, intermediates or final product, or moving non-value steps out of the main production flow – for instance, cleaning-in-place (CIP) and sterilisation-in-place (SIP).

Batch Size

The size of a facility is directly related to its production capacity. If a facility is smaller, then its capacity or the amount of product

Keywords

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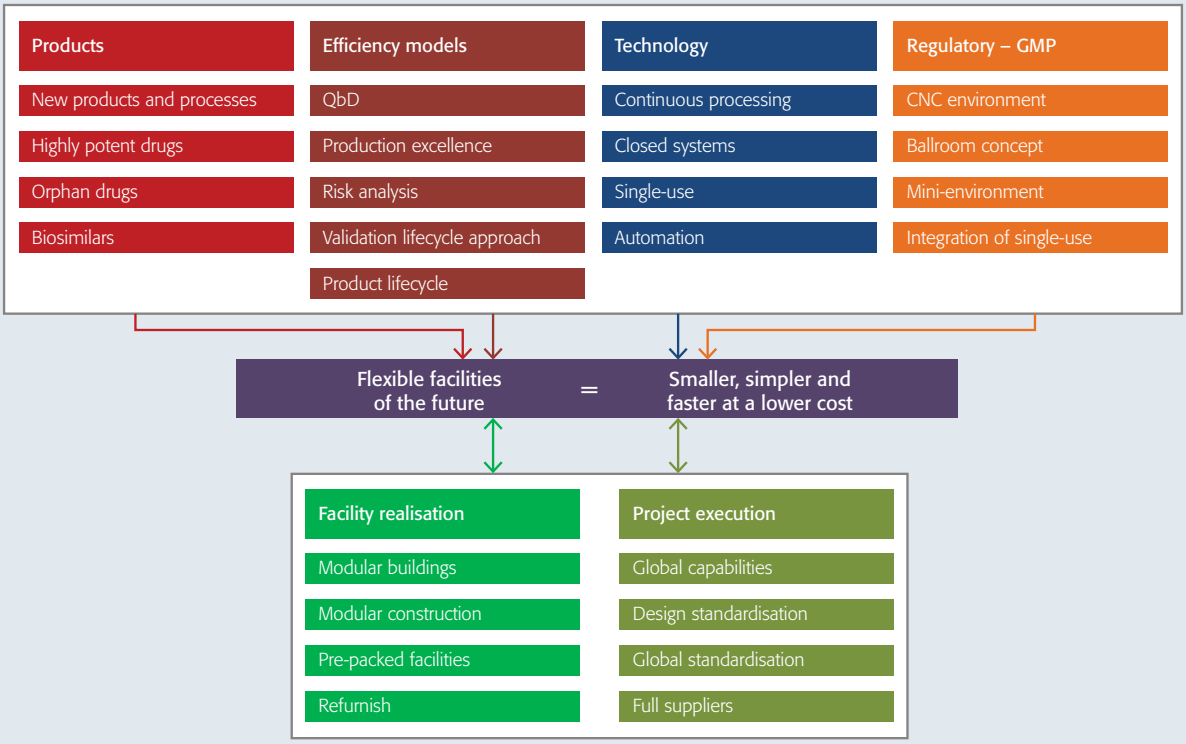

Figure 1: Factors contributing towards more flexible facilities

demand should also fall. Industry estimates show that the number of new blockbusters has decreased in contrast to the recent success of new orphan drugs and antibody drug conjugates, and that many companies also have a developing interest in biosimilars. In all of these cases, a smaller capacity should satisfy production demand.

The contrary is also true. Greater product titres and downstream throughput require a smaller batch size, while maintaining a high production capacity.

In parallel, following production excellence principles, there may be a shift from volumetric production to production intensification. In other words, rather than producing the yearly quota in large bioreactors in just a few batches or building up large inventories of product, the industry may turn to reducing batch size and adjusting production to match just-in-time demand. Moreover, the introduction of continuous processing should also lead to a decrease in the number and size of production equipment (1).

Simpler Facilities

A smaller batch size brings smaller production equipment, which in turn translates into mobility. Large, fixed equipment that requires having the building designed around it should be replaced by small, mobile equipment that can be rolled into almost any large space. The implementation of single-use equipment can further minimise the number of utilities – CIP supply and return lines, or steam and condensate lines for SIP, for example. It is, then, unsurprising to hear that unused industrial buildings are increasingly being retro-fitted into biopharma production facilities.

Quite apart from removing non-value steps from the production floor, single-use equipment is non-fixed and mobile, so can be easily relocated. This allows for easy reconfiguration of processes, or even the replacement of the machinery. With lowering investment costs and the need for constant development,

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equipment should support the upgrade of production trains to the latest technology.

The implementation of closed systems represents one of the biggest visual changes to the production floor. If products are not exposed to the immediate room environment, there should be no concerns regarding contamination or cross-contamination within the atmosphere. With a robust risk assessment in place to validate this, it should be possible to move production outside the cleanrooms – for example, in controlled non-classified (CNC) spaces – and unify products in one single production hall, also known as the 'ballroom'.

Faster at a Lower Cost

If facilities are becoming smaller and simpler, it is expected that their deployment will be faster and at a lower cost. Without a large control area or major heating, ventilating and air-conditioning installation, and with minimum utilities, facilities will not require long design phases or large engineering teams. The primary focus can then move to the construction phase, in order to guarantee a fast and economic realisation on a global basis. For this reason, modularity is coming to the fore, and engineering construction companies are well-positioned to implement these facilities worldwide to a consistent standard and identical quality.

In light of this, it is unsurprising that pre-packaged modules – like KUBio from GE Healthcare or PODs from G-CON Manufacturing – are on the market. Here, the facility becomes a product in itself and is offered directly by the equipment supplier, providing a complete solution from one source. However, the challenge is to construct such a facility in less than 15-18 months, while requiring an investment of under $30 million.

Current View

Even if production is not the largest factor in determining the final product price, the efforts necessary to shape a new biopharma facility are huge. Ultimately, the facility should not be an obstacle to in-time product delivery to the evolving global market.

With such huge resources being expended, the results must prove successful. Manufacturing excellence is more applicable on the production floor, but it is not clear if QbD provides the expected benefits at a reasonable price (2,3). As closed systems are not a new concept, their potential is well-described, promoted and, at present, being applied (4-8). However, this approach still generates strong controversy and discussion – particularly with regard to the ballroom concept – and alternatives are being put forward (9).

In the end, the imperative need to prove that a scientific approach and modern tools are equal to, if not better than, past practices will remain the biggest hurdle. But even with this overall resistance, biopharma production facilities are undeniably undergoing a transformation.

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