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5 – 7 November 2019 | Frankfurt, Germany

Manufacturing evolution:
How manufacturing tech is adapting to changing pharma needs

The technologies pharma uses to make drugs are evolving in line with shifting industry priorities, stricter quality regulations and the ever-present drive for cost efficiency, say experts.

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Executive Summary

Competition in the generics sector is increasing demand for technologies that can manufacture large volume drug products faster and more efficiently. There is demand for everything from better powder flow and containment systems through to faster fill, finish and packaging technologies.

In addition, the small molecule drug sector's desire to differentiate its products – for example by employing modified release systems – has increased demand for systems capable of manufacturing such formulations. Examples include various extrusion, spray drying and blending technologies.

Pharma interest in continuous manufacturing is also an opportunity for technology developers. There is particular demand for systems with enhanced connectivity and monitoring capacity.

The emergence of the personalised medicines and cell and gene therapy sectors has also created demand for technology innovation. Modular technologies with reduced footprints are best suited to the smaller production runs that are characteristic of personalised medicines. In addition, AI systems have a role to play in the enhanced process monitoring and data management that the production of such therapies requires.

Chemical origins

The pharmaceutical sector has its origins in the pharmacies and chemical industries of the 19th century. Germany's Merck, for example, began as a pharmacy while Pfizer was founded as a dye maker in 1849 [1].

These origins have influenced the modern drug industry, in particular in areas like production where, until recently, the focus has been on volume.

However, the past few decades have seen a shift in priorities. The 'patent cliff' – which saw many blockbuster drugs lose IP protection – increased both opportunities and competition in the generic drug sector, driving demand for faster, more efficient manufacturing.

The patent cliff also prompted innovative drug firms to focus on complex, hard to copy biopharmaceutical products. This has also stimulated the development of new manufacturing technologies.

A spokesperson for the MHRA – the UK Government agency tasked with making sure drugs and devices are safe - confirmed the shift, telling us "The most active areas of innovation are for Advanced Therapy Medicinal products (ATMPs) which comprise gene therapy, cell therapy and tissue engineered products and cover a range of manufacturing technologies."

Facility design

In 2013 the MHRA set up its "innovation office" with the aim being to "help organisations of all backgrounds and sizes, including academia, the NHS, SMEs and individuals, to develop "innovative medicines, medical devices or novel manufacturing processes." Part of this involves advising on facility design and technology selection [2].

The EMA spokesperson told us "The principles for design and use of manufacturing facilities are set out in *EU GMP*" adding that "The basic GMP principles are that the products are of the appropriate quality – this means that they meet the specifications set out in the Marketing Authorisation of the product, or those set out in the Clinical Trial Authorisation. It also means that the product should not be cross-contaminated with any other product."

Such initiatives are vital says John Milne, training director at Ireland's National Institute for Bioprocessing, Research and Training (NIBRT), who told us, "Proper facility design equates overall success."

Milne cited gains made in cell culture performance as a driver, explaining that,

"Emerging modular and more mobile strategies will allow manufacturers to transfer from large capitally intensive facilities to smaller, more flexible and even in time standardised facility design. The emergence of larger "ballroom" style areas where unit operations that traditionally were separated can now take place using functionally closed systems in relatively close proximity is striking."

Manufacturing technology developers are responding according to Milne, who told us "The many innovations being developed by key vendors in the space is testament to this approach.

He also predicted that further growth of the personalised medicines sector will see more developers use modular production facilities and smaller, single-use manufacturing systems.

Beyond the batch

Elsewhere, the desire for manufacturing efficiency has sparked interest in new production approaches which, in turn, is driving technology innovation.

In 2016, for example, the US Food and Drug Administration cleared Janssen to start making its HIV drug Prezista (darunavir) using continuous manufacturing, in addition to batch [3]. At the time Rutgers University, which helped the J&J unit develop the technologies required, said the aim was to achieve [4]:

"improvements in quality, safety, efficiency, cost, and speed to market."

And further development will be the key to continuous manufacturing's wider adoption says Milne. "While much of the infrastructure is currently in place or perhaps shortly will be in place to facilitate a transition toward continuous manufacturing, developments are still required to fully realise the potential of this technology."

He cited the need for better technology integration as critical.

"The key challenge with integrated continuous manufacturing strategies is the need for reliable and meaningful process analytical technologies (PAT), that can provide evidence that the key quality attributes of a product are being controlled in what will be a continuous manufacturing process."

Milne added that, "QBD initiatives favoured by regulatory agencies are predicated on the availability of reliable PAT technologies and there is still a journey to take to develop such capabilities."

Those in favour say AI

Improving how technologies communicate and share data is also a focus for developers of systems used in batch-wise production.

Many efforts are centred on applying artificial intelligence according to Milne, who told us "It is clear manufacturing scenarios in the future will utilise newer concepts and the success of the wider Manufacturing 4.0 concept will be dependent on such initiatives.

"Facilities are becoming more digitised and the management of greater amounts of data to predict process performance and output is becoming more critical. In process development activities new tools are being deployed to develop a greater process understanding and route to process scale-up."

The key question, according to the MHRA, is how the drug industry will use the manufacturing data that is generated.

The organisation's spokesperson told us "What has changed has been the need to assure the integrity of the data, typically referred to as data integrity for which MHRA has produced *guidance* and which

is aligned with that produced by others including the FDA and the World Health Organisation."

Cell and gene therapies

In the past few years several cell and gene therapies have been approved, with Yescarta, Luxturna and Kymriah being the obvious examples.

The emergence of such therapies has also impacted the manufacturing technology sector, albeit to a limited extent. According to the MHRA's spokesperson much of the focus has been on repurposing existing systems.

"Most of the technologies used in their manufacture have been taken from those established in pharmaceuticals as well as those regulated under transplants and transfusions. The challenge has generally been to adapt them for what is largely a small scale of operation since many are for use in individual patients so the challenges are largely an issue of scale out rather than scale up".

This is also the view of John Milne from NIBRT, who told us "By nature such treatments are niche and most often small scale in focus. Such processes will be facilitated in modular flexible facility designs utilising new innovations from vendors.

"The real challenge with such personalised technologies is building scale into what can often be time consuming and labour intensive manufacturing campaigns. In the case of viral vector production processes that will need to be scaled-up, traditional cell culture configurations that are well accepted will be used to propagate viral vectors so the transition may not be necessarily as troublesome, albeit the purpose of the cell culture phase is different."

Ultimately, the successful production of advanced and personalised meds will depend on new techs according to Milne, who says industry and its suppliers must ensure these systems are implemented in an effective and compliant manner.

References

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