A Continuous Education

Much has been made of the potential of continuous platforms to supplant traditional pharmaceutical batch manufacturing and drive down API production costs. But how suitable is the technology to the precise requirements of complex pharma processing?

Gareth Carpenter | Jun 12, 2020

The sheer complexity involved in producing active pharmaceutical ingredients (APIs) means that up until now, the industry has relied for the most part on the traditional method of batch manufacturing. This step-by-step process which requires the completion of each batch before

moving on to the next is not very time-efficient and often requires the use of numerous pieces of machinery.

The method is not without its advantages; the technology is generally less expensive to set up initially and each batch process can be tailor-made uniquely depending on which materials are being used. In some cases, this is a cast-iron requirement due to the composition of certain products and materials.

Batch manufacturing's dependence on mainly large-scale, labour-intensive equipment, has over time led to a shifting of API production away from the developed US and European markets to emerging one such as China and India, where labour costs are low.

Saving money and time?

However, interest in and adoption of continuous manufacturing of APIs is gathering momentum, not least due to its promise of substantial cost savings and increased time efficiencies, and ability to take a product seamlessly from the raw material stage to the finished product stage.

While not a particularly new technology – it has served other industries for several years – uptake of continuous manufacturing by the pharma sector has been slow. However, it could yet play a pivotal role in reshaping the supply side of the global API market. With the current coronavirus pandemic highlighting the pharmaceutical supply chain's reliance on cheap-labour markets such as China and India, there are concerted moves – particularly in the US – to relocate API manufacturing domestically.

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In May, the US government signed a USD 354 million contract with pharma start-up Phlow Corporation to manufacture generics and APIs needed for drugs in short supply, including COVID-19 treatments, in a move to create the nation's first strategic stockpile of key ingredients and reduce its dependence on overseas supply. Under the terms of the agreement, Phlow will lead a team of private sector entities that includes API and intermediates manufacturer Ampac Fine Chemicals, Civica Rx and the Medicines for All Institute.

Maximising throughput

Virginia-based Phlow has set its stall out in no uncertain terms, promising that all its pharma products will be made by continuous manufacturing and heralding the technology as a modern process "that maximizes throughput, increases productivity, and lowers labour requirements."

Dr Frank Gupton is co-founder of Phlow, chair of Virginia Commonwealth University's (VCU) Department of Chemical and Life Science Engineering and CEO of the Medicines for All Institute and will head up the strategic partnership.

He says that one of the biggest reasons why the pharma sector has been slow to adopt continuous manufacturing is that looking at the overall picture of capital investments in batch manufacturing, "there hasn't been a real burning bridge to switch over; when you look at the cost of active ingredients, they are only a small percentage of the overall price of the drug."

"The emphasis is more on time to market than it is on optimising these processes so they become an extension of the laboratory where you develop a round-bottom flask process and then it can take some extra time to convert it over to continuous, as opposed to going to a big round-bottom flask like a 6,000L reactor," he says.

Gupton adds that on top of this, there exists a level of uncertainty with regards to regulatory constraints: "I know that top management at the Food and Drug Administration is committed to supporting this movement towards continuous

manufacturing, strictly from the standpoint of reproducibility. The challenge at the operational level is that there aren't that many FDA inspectors who have seen a continuous process and know how to inspect for it so there's a learning curve from the FDA 's perspective in that they're going to have to come up with training for their inspectors."

Switching mid-programme not an option

According to Bikash Chatterjee, Chief Operating and Science Officer at Pharmatech Associates, one of the biggest reasons why continuous manufacturing has not been broadly adopted in pharma is that the decision to do so needs to be made at the get go.

"It is very difficult to switch strategies mid-program," he explains. "Arguing that the material that was in the animal safety studies or pre-clinical lots is fundamentally the same material that's being put into commercial products gets more complicated to do when you switch from batch to continuous manufacturing."

One key trend within the industry over the last decade or so is the shift toward more targeted precision medicines with smaller patient populations and lower daily dosage, which can reduce annual demand for the requisite APIs to just a few hundred kilogrammes. How does this square with the common conception of continuous manufacturing as a means of scaling up and producing bigger yields?

"People tend to think of continuous manufacturing as something that you have to do only on a large-scale, with metric tons of material, but the reality is you can do it at small scale and have exquisite control," says Chatterjee, explaining that the principles around continuous manufacturing are really scale-independent.

"We're really talking about enhanced control; demonstrating that you understand the process to the point that you can establish a control strategy which allows you to have confidence that the characteristics of the output of that process are going to

behave as they should. It doesn't matter if you're doing this at hundreds of tons of material per minute or milligrams per minute," he adds.

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Gupton argues that utilising continuous manufacturing presents an interesting opportunity for pharma companies with potent compounds in their portfolios. He explains that highly potent low dosage drugs are difficult to make in batch due to the need to reduce exposure to employees when running processes as well as the restrictive complications around cleaning between batches.

"You could have a small continuous unit running inside a glove box that would allow you to make your annual requirement of the drug, minimise the exposure and run it on dedicated equipment," he says. "Almost everybody's considering that the high-volume drugs where the markets are well defined are the ones most amenable to building a unit that is continuous. That's true but I also think this other emerging opportunity does lend itself to a continuous mindset."

While driving down the cost of API production is often seen as a key motivator for adopting a continuous platform over batch, Mr Chatterjee insists that companies may have higher priorities.

"At some scale, continuous manufacturing affords some cost savings because you don't have all of the overhead and infrastructure associated necessarily with batch, but the strategy here is not about cost, it's about consistency, capability and speed and that's where I think continuous platforms could really be a silver bullet for some of these major drugs," he says, citing antibiotics and antivirals being used as treatments for COVID-19 as prime examples.

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Gupton says continuous manufacturing is just one element of Phlow's holistic model which he describes as an "end-to-end system" which begins with making the essential chemical-based "building block" starting materials all the way through to utilising Civica Rx, a non-profit organisation that emerged in response to generic drug shortages and which he describes as "a direct supply chain into the US hospital systems."

Routine adoption?

Whether continuous manufacturing of APIs will become routinely adopted by pharma companies is still a matter for debate, but Chatterjee believes that the industry now has the right instruments at its disposal to make this outcome more likely.

He says that the sophisticated ability of artificial intelligence and machine learning to collect and analyse data makes understanding exactly where the product is during the process at any given time that much easier.

"We are probably better positioned than we've ever been in the last 50 years to see a broader adoption of continuous manufacturing around the world because the tools that we have to gather and manage the data are the most mature they've ever been in our industry," Chatterjee adds. "Initiatives such as Pharma 4.0 are excellent in illustrating how we can utilise intelligent technology to try and gather the information we need to demonstrate our technical argument, that we understand what's happening in the process."

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