

Guest Editorial

Continuous Manufacturing at Johnson Matthey For Pharmaceutical Applications

The productivity and efficiency of continuous manufacturing have long been exploited for benefit in bulk chemical production applications. For decades chemical manufacturers have put continuous manufacturing processes to good use, producing millions of metric tonnes annually utilising a relatively small manufacturing footprint. Often tens of per cent of the global production of large volume products are processed through only one or a few facilities.

In years past, drug manufacturing has been done exclusively *via* batch processing methods. In fact, until recently, no commercialised drugs were produced with continuous manufacturing methods. Over the past fifteen years, some pharmaceutical groups have begun to explore the potential for employing continuous manufacturing methods in drug manufacturing. And in the past three years, those efforts have begun to accelerate with the deployment of continuous manufacturing methods across the pharmaceutical industry increasing rapidly. The majority of the top 20 large pharmaceutical companies now have programmes ongoing in the area ranging from early-stage exploratory research to full-scale transformation of commercial processes. Eli Lilly and Company, for example, has recently made a US\$40 million investment to build a continuous manufacturing facility at its Kinsale, Ireland manufacturing plant.

Drivers for Adoption

One of the historical factors that have contributed to the slower adoption of continuous manufacturing in the pharmaceutical industry has been uncertainty around the regulatory pathways for approval by the authorities. All commercialised drugs must be manufactured by a process which the regulatory authorities have approved. Recently, the tide here has

begun to change. The best evidence of this are two recent US Food and Drug Administration (FDA) approvals for drugs employing continuous manufacturing processes. In 2015 Vertex Pharmaceuticals Inc received approval from the FDA for its cystic fibrosis drug Orkambi[®] which employed a continuous manufacturing process. Later, in 2016, Janssen Pharmaceutica submitted and received approval for an updated process for the human immunodeficiency virus (HIV) drug Prezista[®] utilising a continuous manufacturing process. At the time Lawrence Yu, PhD, the FDA's deputy director of the Office of Pharmaceutical Quality (OPQ) in the Center for Drug Evaluation and Research (CDER), wrote on the FDA's blog: "Although it is not easy for drug manufacturers to transition from batch to continuous manufacturing, there are significant rewards. FDA encourages others in the pharmaceutical industry to consider similar efforts" (1). While these words were indicative of the agency's warming to the prospect of continuous manufacturing in the production of drugs, an official guidance document from the FDA was absent. Such guidance documents are the chapter and verse against which pharmaceutical companies are measured in regulatory approvals. In February of 2019, a Draft Guidance for Industry on the Quality Considerations for Continuous Manufacturing was issued by the FDA (2).

While lower confidence in the acceptance of continuous manufacturing processes by the regulatory authorities has historically slowed adoption by the pharmaceutical industry, there are other unique factors relating to drug manufacture that have also played a role. Primarily these are low production volumes, low contribution costs of manufacturing relative to the overall cost of developing, launching, and marketing a drug and payback periods for the

investment which are truncated by patent life expiration.

This results in many different drivers for the adoption of continuous manufacturing in the pharmaceutical industry compared to bulk chemical manufacturing. In the pharmaceutical industry today the drivers to adoption of continuous manufacturing are speed, scale-flexibility, quality and safety. While efficiency is important, the tradeoff for speed and flexibility is more important. With first-to-market pressures always looming, companies have strong motivation to develop a manufacturing process as quickly as possible. One of the unique attributes of continuous manufacturing is its ability to deliver product at a variable scale with consistent quality. Increases in production scale of one, two and even three orders of magnitude can be supported by either scaling up the continuous manufacturing process or numbering-up the continuous manufacturing production units. These sorts of production increases are becoming very common in the life of new pharmaceutical products. Often new products are developed for an initial therapeutic indication, one which has fewer treatments available for instance but may have a smaller patient population, and later the drug is expanded to other much larger indications. This can mean a drug launches with an annual volume requirement of 50 kilograms per year yet within one to two years, if the next indications are successful, the volume requirements can increase to 5 metric tonnes per year. Regulatory requirements mandate that the quality profile of the active ingredient be the same regardless. Thus, there are strong motivations to keep the manufacturing process the same and continuous manufacturing lends itself well to this.

Collaborating for Continuous

Johnson Matthey has adopted the use of continuous manufacturing in the products it produces for the pharmaceutical and medical industry and in the services it provides to pharmaceutical companies. In addition, in September of 2017 Johnson Matthey created a partnership with a Massachusetts based company named Snapdragon Chemistry Inc which was spun out of Massachusetts Institute of Technology (MIT) to focus on the design of continuous manufacturing processes for application in the pharmaceutical industry.

Through that relationship, we can combine Snapdragon's early stage data-rich platform for chemical route scouting and design with Johnson Matthey's expertise in process development, scale up and manufacturing according to current good manufacturing practices (cGMP).

The Snapdragon laboratories are near to Johnson Matthey's Devens, MA facility where we have development laboratories, kilogram-scale laboratories and a GMP manufacturing plant. This is where we do most of the development work for the pharmaceutical sector. The proximity allows for optimal interaction with our staff spending time at Snapdragon's facility and its staff spending time at our facility while we are working together on a project.

We have applied continuous manufacturing to multiple projects together and have just kicked off a new project. We also have a pipeline of the next opportunities we are discussing with customers. It's an exciting time as the pharmaceutical market moves toward wholesale adoption of innovation in the way drugs are manufactured, including *via* continuous manufacturing. It is yet unclear just how different drug manufacturing in the future will look to today, but one thing seems clear: that continuous manufacturing will play an important part in the transformation. We are very excited for Johnson Matthey to be part of this evolution.

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References

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