Modernising pharmaceutical manufacturing

The United States Food and Drug Administration (FDA) recently published new draft guidance on the implementation of emerging technologies, with the objective of modernising the manufacturing base within the pharmaceutical industry. The FDA sees this initiative as part of the long-term solution to avoid drug shortages, which have plagued the US market in recent years as well as meeting an ongoing commitment to modernise manufacturing practices. The objectives are twofold—to encourage early adoption of novel technologies and to ensure that regulatory review is based on state-of-the-art science.

The FDA indicated that for the purpose of this guidance, the term ‘manufacturing’ also includes testing, quality control, packaging and labelling operations. The agency’s guidance on process validation also encourages process improvement and ongoing innovation, including continuous manufacturing. Modernising the manufacturing base needs to be underpinned by an integrated approach to product and process understanding supported by real-time process analytical technology (PAT), the FDA believes, which taken together should support better understanding supported by real-time process analytical technology to be underpinned by an integrated approach to product and process understanding supported by real-time process analytical technology (PAT), the FDA believes, which taken together should support better understanding, monitoring and process control. The key concepts underpinning PAT are “multivariate data acquisition using process sensors and analysers, process monitoring and subsequent control and supporting management tools”.

The regulatory approach within the European Union has been broadly similar, although there has been less overt focus on the role of modernising the manufacturing base. The European Medicines Agency (EMA; formerly known as EMEA) introduced a PAT Team in 2003 to support PAT and Quality by Design initiatives within the EU. Subsequently, it issued guidance on process validation, which supports the application of continuous process validation. Although not necessarily linked, continuous manufacturing often results in real-time release testing (RTRT).

Continuous manufacturing

Continuous manufacturing is where the input materials are continuously added at the beginning of the process and the product is continuously discharged at the end of the process. In contrast, a classical batch system is where input materials are discretely added and the resultant product is separately removed at the end of the process.

Continuous manufacturing is expected to result in a reduction in the number of process steps, less bulky equipment and a commensurately smaller manufacturing footprint. Processes will typically run 24/7 for the entire year, with a one-two week planned maintenance downtime. Continuous manufacturing offers significant advantages in terms of cost, efficiency and robustness (it reduces failure rates and decreases in level of ‘stock-outs’), as well as introducing significant flexibility into manufacturing facilities. As a result of the increased in-process monitoring via PAT tools, there is an increased likelihood for real-time quality data, potentially resulting in RTRT.

MIT-Strathclyde universities recently published a series of white papers highlighting the current state of thinking in continuous manufacturing. In addition, the International Conference on Harmonisation (ICH) is developing a new guideline for Pharmaceutical Product Lifecycle Management, which is seen by many as a basis for meaningful implementation of continuous manufacturing across the industry.

The logical first step in continuous manufacturing is to facilitate it by modifying the existing batch process. This is often termed heterogeneous manufacturing, where output from the primary drug substance process is not aligned with the requirements of the secondary drug product processes. Certain manufacturing operations already align themselves with continuous manufacturing, for example, roller compaction and hot melt extrusion. In roller compaction, powders are continuously fed into rollers, producing compacted ribbons, which are continuously fed into a mill, which produces a dry granulation blend, suitable for compression. Similarly, in hot melt extrusion, the input materials are either pre-mixed or separately fed into an extruder. Within the heated extruder barrel the materials are softened, mixed and then extruded as a solid dispersion; this extrudate is then shaped, cooled and further processed (if required). The desired future state would be a homogenous process, whereby the blend has the desired properties engineered into it in order to manufacture the drug product.

In conclusion, continuous manufacturing offers some very significant advantages and in parallel the opportunity to modernise the pharmaceutical industry. For example, it could preclude the necessity for costly and problematical scale-up, i.e., an annual output of 1 billion tablets equates to about 120,000 tablets per hour and this is a scale that is typically used during development. Thus, developing a commercially aligned process would not necessarily require scale-up considerations and pivotal clinical supplies could be taken during validation of the continuous manufacturing process.

References

1. References can be found online at: www.europeanpharmaceuticalreview.com