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Special Topic Commentary

Regulatory Perspectives on Continuous Pharmaceutical Manufacturing: Moving From Theory to Practice: September 26-27, 2016, International Symposium on the Continuous Manufacturing of Pharmaceuticals

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ABSTRACT

Continuous manufacturing plays a key role in enabling the modernization of pharmaceutical manufacturing. The fate of this emerging technology will rely, in large part, on the regulatory implementation of this novel technology. This paper, which is based on the 2nd International Symposium on the Continuous Manufacturing of Pharmaceuticals, describes not only the advances that have taken place since the first International Symposium on Continuous Manufacturing of Pharmaceuticals in 2014, but the regulatory landscape that exists today. Key regulatory concepts including quality risk management, batch definition, control strategy, process monitoring and control, real-time release testing, data processing and management, and process validation/verification are outlined. Support from regulatory agencies, particularly in the form of the harmonization of regulatory expectations, will be crucial to the successful implementation of continuous manufacturing. Collaborative efforts, among academia, industry, and regulatory agencies, are the optimal solution for ensuring a solid future for this promising manufacturing technology.

Introduction

Continuous manufacturing is a key enabler for modernization of pharmaceutical manufacturing. This emerging technology has the potential to improve agility, flexibility, and robustness in the manufacture of pharmaceuticals. As expected, with the introduction of new technologies in the pharmaceutical sector, there are regulatory uncertainties in adopting a continuous manufacturing process. These include material traceability, process design, monitoring, and control that require consideration beyond established practices. More importantly, some uncertainties exist regarding how product quality is evaluated and assured in the context of continuous manufacturing technology within the current regulatory frameworks. To meet these challenges, key stakeholders, including drug manufacturers, suppliers, research institutions, and regulatory agencies, met at the 1st International Symposium on Continuous Manufacturing of Pharmaceuticals (ISCMP), sponsored by the Novartis-MIT Center for Continuous Manufacturing and the Continuous Manufacturing and

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Crystallisation Consortium on May 27-28, 2014 to discuss existing knowledge, opportunities, challenges, technology gaps, and regulatory aspects related to continuous manufacturing. The meeting resulted in a series of White Papers intended to drive the pharmaceutical industry toward reaping the true benefits of continuous manufacturing and adopting this emerging technology.[1-8]

The pharmaceutical industry, research institutions, and regulatory agencies are collaborating to overcome challenges related to the development and implementation of continuous manufacturing. Significant progress has been achieved since the 2014 ISCMP. Nearly all major innovator pharmaceutical companies are working on continuous manufacturing technologies. Only 2 years have passed since the first symposium, and already there have been tremendous advances in terms of the number of companies committed to continuous manufacturing. The degree of their commitment can be measured by the number of continuous manufacturing projects that they are pursuing. Of the top 15 pharmaceutical companies, nearly all have publicly declared their commitment to continuous manufacturing. The number of continuous equipment vendors is increasing. Most significantly, the U.S. Food and Drug Administration (FDA) approved Orkambi (lumacaftor/ivacaftor), which is a new cystic fibrosis drug produced using continuous drug product manufacturing methods (i.e., the active pharmaceutical ingredient [API] is still produced via batch) including real-time release testing (RTRT). In 2016, the US FDA also approved a manufacturer's switch in its production method from batch to continuous drug product manufacturing for the existing product Prezista (darunavir). These 2 examples represent a significant step in integrating continuous manufacturing into commercial pharmaceutical production. They illustrate the feasibility of using continuous manufacturing for a new drug development and commercial production under an accelerated regulatory pathway and for implementing this emerging technology for manufacturing existing products as post-approval changes.

Building upon the 2014 ISCMP meeting and consequential implementation progress, the 2nd ISCMP meeting was held on September 26-27, 2016. The objective of the 2016 ISCMP included providing real case studies from stakeholders to illustrate progress that has been made since 2014, identifying the remaining gaps, and developing appropriate solutions and next steps to address them. In addition, the symposium aims to develop and provide practical guidelines based on real case studies to support a future International Conference for Harmonisation (ICH) guidance on continuous manufacturing. This paper represents the main output of the 2016 ISCMP. In support of the 2014 Regulatory White Paper,[1] this paper will not repeat the detailed regulatory and quality issues previously described in the 2014 paper, but will instead focus on providing updates on topics specifically discussed during the 2016 meeting, including scientific and regulatory aspects related to the development, implementation, and evaluation of continuous manufacturing from both industry and regulatory agency perspectives. In addition, this paper identifies opportunities to further advance and accelerate the implementation of continuous manufacturing for pharmaceuticals.

2016 Symposium Summary

As this White Paper is based on the 2nd International Symposium on the Continuous Manufacturing of Pharmaceuticals held in Cambridge, MA, September 26-27, 2016, the technical summary below is based on the presentations and discussions of the symposium. This summary includes specific discussion points, but without noting the specific sources.

Advances Since 2014

On the small molecule side, the primary focus has been on drug product, specifically on wet granulation and direct compression, with continuous coating starting to pick up in practice. More than two-thirds of the companies involved have integrated continuous drug product trains from equipment vendors, and the remainder has separate continuous unit operations. Many existing and new equipment vendors continue to play an important role in the design, construction, and implementation of continuous manufacturing equipment. Work on the continuous manufacturing of API is also increasing substantially, especially on the reaction technology side. Continuous crystallization has yet to demonstrate pickup in practical implementations in the industry beyond laboratory scale. Companies tended to focus either on drug substance or drug product, and there were significant advancements, with concurrent benefits, demonstrated both for continuous chemistry and workup as well as for continuous granulation leading to final dosage form and for direct compression.

In general, engagement with regulatory authorities went well, which should lead to greater confidence that new continuous manufacturing approaches will not be hindered by regulatory issues. Despite this, it became clear that regulators are learning alongside practitioners. Interaction early and often with regulatory authorities was key to a smooth regulatory review process and timely approval. Regulatory authorities were familiar with and open to discussing the intricacies of quality by design (QbD), process analytical technology (PAT), RTRT, and continuous manufacturing in general. There has been significant progress made by several companies in developing control strategies that take into account specific limitations, leading to RTRT.

In the bioprocessing area, there are several new facilities being developed with continuous manufacturing capabilities, although they are not designed specifically for end-to-end continuous bioprocessing. There is now a successful fully integrated continuous bioprocessing demonstration facility for drug substance and several plug and play facilities with integrated PAT, both for monoclonal antibodies (mAbs) and other therapeutic protein production. Many technology suppliers are developing process units intended for continuous operation.

Challenges and Opportunities

Most innovations involve the continuous implementation of existing technologies, including PAT, as opposed to development of new technologies. These innovations are either for parts of manufacturing process or only one section (drug substance or drug product). These should still be considered major advances, particularly considering the number of processes that are being developed with continuous components and the value demonstrated for doing so. It seems most practical for advancement to occur systematically, as opposed to all at once. Although the PAT technologies can certainly be advanced, there are many available and current PAT technologies that are in no way exploited to their full potential. A key aspect of utilizing PAT tools is determining what the key parameters are to measure. Advances in continuous manufacturing offer opportunities to include enhanced development and process understanding, for example, through detailed mathematical models. It is desirable to develop common approaches of modular platforms and control architectures to facilitate a broad adoption of continuous manufacturing within the industry.

Continuous bioprocessing, while still behind small molecule continuous processing, is starting to catch up. The greater possibility of platform processes for biological molecules or products, mAbs