ARTICLE

CHEMISTRY, MANUFACTURING, AND CONTROLS

Understanding New Guidelines for Continuous Manufacturing

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A Sponsor's Guide to the Implementation of Continuous Manufacturing

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Introduction

With the recent issuance of ICH Q13 Continuous Manufacturing of Drug Substances and Drug Products Final Guidance and subsequent FDA Guidance for Industry in March 2023, sponsors now have a formal framework for implementing elements of continuous manufacturing (CM) into their process.

By implementing these measures, sponsors have the opportunity to shorten their drug approval time and save both time and money in production costs. In this article, we will discuss key elements of the new regulatory guidance and how your organization can begin implementing concepts of CM in your manufacturing process.

Background

Over the past several years, continuous manufacturing processes have become the more innovative and modern approach to drug manufacturing when compared to traditional batch manufacturing.

Continuous manufacturing enables pharmaceutical manufacturers to make more product in a shorter amount of time, thus presenting a direct solution to the ongoing issue of drug shortage while reducing manufacturing costs related to product loss during standard batch processing.

However, there has been little regulatory guidance or framework for companies to reference to implement CM concepts.

Batch Manufacturing

Batch manufacturing has been the standard process used in the pharmaceutical industry for more than a half century. This process follows a step-by-step procedure, designed for a specific drug, starting with a chemical intermediate or cells, and ending with a finished drug or biologic product. This process enables the production of specific amounts of a drug, which can be adjusted to meet market demand.

Continuous Manufacturing

The continuous manufacturing approach has primarily been implemented by pharmaceutical companies who have implemented the process on products prior to NDA approval. The investment required to build dedicated facilities for continuous manufacturing can be very costly and may not be practical for organizations who manufacture multiple types of drugs with various inputs, production times, and market demands. However, there are many ways for sponsors to implement elements of CM without breaking the bank. To emphasize the importance and potential of CM, Zion Market Research predicted that the global pharmaceutical CM market will surpass $3.24 billion by 2028, with a CAGR of around 9.6% from the forecast period beginning in 2021[i].

Highlights of new Regulatory Guidance

In November 2022, the International Council on Harmonisation (ICH) Q13 guidance was adopted by Regulatory Members of ICH. In March 2023, the FDA issued their own regulatory guidance Q13 Continuous Manufacturing of Drug Substances and Drug Products. This guidance applies to CM of drug substances and drug products for chemical entities and therapeutic proteins. It is applicable to new drugs, generic drugs, and biosimilars, including the conversion of batch manufacturing to CM for products already approved on the market.

For these types of products, concepts of CM can be implemented to some or all unit operations. For example, one process can operate in batch mode while others are integrated and operate in a continuous mode.

Other key recommendations from the guidance include:

Define batch size: CM guidance defines this in multiple ways and even allows for alternative approaches based on scientific justification.

Develop a control strategy for CM: These aspects are outlined in ICH Quality guidelines and include demonstrating a state of control, process dynamics, material characterization and control, equipment design and system integration, process monitoring and control, material traceability and diversion, and process models.

Follow critical steps (for manufacturers who are making changes to their overall production output): By changing run time, mass flow rates, or equipment, each modification is assessed by the risk to the overall control strategy. Additionally, manufacturers may scale-out their production by replicating an integrated CM production line or implementing parallel units on the same production line or increasing their existing equipment capacity. Again, the key here is assessing the risk to the overall control strategy.

Implement continuous process verification: This can be achieved using Process Analytical Technology (PAT) and other tools which generate real-time results. The recent Q13 guidance includes several examples of manufacturing and testing approaches for an integrated CM[ii].

How do Sponsors implement CM into their dossier?

Similar to a traditional 3.2.S or 3.2.P section of the common technical document (CTD), companies can easily integrate the overall CM process into these sections. Comprehensive information on the control strategy should be included in sections 3.2.S.2.6 and 3.2.P.2.3, respectively. This will include elements such as material traceability, material diversion and collection strategy and sampling strategy and frequency. For the manufacturing process and process controls section, the flow diagram will need to include a clear indication of the continuous and batch processing steps as well as when PAT measurements, feedforward or feedback process controls are conducted. The guidance provides clear recommendations for including CM-related information in your CTD[ii]. While the guidance offers a solid framework, this process should include Regulatory-CMC subject matter experts to help strategically guide the implementation of CM into your process.

Evaluating if CM is right for your product and organization

There is no such thing as a "one-size fits all" approach in pharmaceutical manufacturing. Every organization and manufacturing process of a drug or biological product is different. Implementing CM is a significant undertaking for any company, regardless of the situation. How do you know if CM is right for you?

There are some questions to ask your organization that may be able to help evaluate this question, including:

Can elements of CM substantially improve at least 2-3 areas of your current batch manufacturing process?

Can you successfully integrate elements of CM without negatively impacting your ongoing manufacturing process?

Will the implementation of elements of CM provide a cost-benefit to your organization in the next 5 years and beyond?

If you answered yes to these questions, then it is strongly recommended that you continue to pursue elements of continuous manufacturing of your product.

Conclusions

Whether your organization is currently in clinical development or has a marketed drug or biologic product, integrating continuous manufacturing concepts into your process is becoming more achievable than ever. As global health needs continue to evolve, continuous manufacturing can help provide a consistent and stable drug supply while also providing a more cost-effective manufacturing process (after start-up costs) for the sponsor. Conducting a thorough evaluation of the product portfolio, both in the commercial market and in clinical development, can help evaluate if and where implementing these concepts could be beneficial. You may consider engaging a third-party with CMC expertise to assist with this evaluation and offer a recommendation. Whether you determine that introducing CM is right for your business or not, it is a step forward in the progression of the industry for FDA to accept and provide guidance on this manufacturing approach which has been successfully used in other consumption industries for decades.

References

[i] PR Newswire, With 9.6% CAGR, Pharmaceutical Continuous Manufacturing Market Size Worth USD 3.24 Billion in 2028, Zion Market Research, June 20, 2022, Accessed April 20, 2023

[ii] ICH Q13 Guidance