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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

should provide tremendous opportunities. Some companies are exploiting those opportunities, while the industry could aim to devote as much attention to continuous bioprocessing as to continuous processing of small molecules. On both the small and biological molecule sides, there are tremendous opportunities to enhance continuous manufacturing via new technologies. These include in the small molecule area: reaction chemistries, reactor designs, workup (including nanofiltration and continuous crystallization), filtering and drying, and formulation design. Close collaboration between chemists and chemical engineers is key to taking advantage of new upstream technologies. New technologies in biologics include new cell lines, extended use fed-batch and perfusion systems, chromatographic systems together with resins, filtration and diafiltration with new membranes, and microbioreactors. Progress has been made with automated control via detailed mathematical models on the bench scale, and great progress could be made on the commercial scale.

Current Regulatory Landscape

Regulatory agencies, including the FDA, European Medicines Agency (EMA), and Japanese Pharmaceuticals and Medical Devices Agency (PMDA), support manufacturing innovation and the adoption of continuous manufacturing for pharmaceutical production. They believe that this emerging technology has the potential to offer an enhanced level of product quality assurance while providing the maximum flexibility and agility for pharmaceutical manufacturers, and that it is strongly aligned with QbD for pharmaceutical development. Generally, there is a consensus that continuous manufacturing can be effectively executed within the existing regulatory framework, and there are no major regulatory hurdles for manufacturers to implement continuous manufacturing.

Although the current regulatory environment is generally supportive of adopting continuous manufacturing for pharmaceutical products, one of the challenges posed is a potential gap in standard approaches for the regulatory assessment of continuous manufacturing processes. Reviewers/assessors and investigators/inspectors need to develop expertise in the new technology to determine the appropriate regulatory approaches. To foster the adoption of innovative technologies including continuous manufacturing, FDA, EMA, and PMDA have each established specialized teams, as summarized below:

- FDA Emerging Technology Team: a multidisciplinary team, including representatives from the FDA quality review and inspection programs, supports and facilitates the implementation of emerging technologies to advance pharmaceutical product design and manufacturing.
- EMA PAT Team: a team, including assessors and inspectors from multiple regions of Europe, supports PAT and QbD activities.
- PMDA Innovative Manufacturing Technology Working Group: a working group, including members from the Office of New Drugs, Office of Manufacturing/Quality and Compliance, and Office of Regulatory Science, establishes PMDA's perspective on the latest technologies of pharmaceutical quality control.

These teams serve as the primary point of contact for each respective agency for pharmaceutical manufacturers interested in employing emerging technologies in the context of developing products for market approval. They also provide a forum for early communications between the agency and manufacturers regarding proposed new technologies during drug development and prior to formal regulatory submission. Due to the innovative nature of continuous manufacturing, it is highly recommended to begin interactions with regulatory authorities as soon as possible to facilitate the implementation of continuous manufacturing.

The FDA is currently supporting collaborative research with academic institutions, government agencies, and companies to promote manufacturing innovation in the U.S. pharmaceutical manufacturing sector. The results of this research effort, together with knowledge and experience gained from evaluating regulatory submissions containing continuous manufacturing, will be used to support science-based quality standards and policies and provide training tools for regulatory bodies for continuous manufacturing. In the case of PMDA, there is a specialized group for continuous manufacturing, which is sponsored by the Japan Agency for Medical Research and Development in Japan. This group consists of members from the PMDA, industry, National Institute of Health Science, and academia. It provides a collaborative platform for discussing issues related to new technology and its regulation.

Key Regulatory Aspects of Continuous Manufacturing

Since the 2014 ISCMP, considerable knowledge and experience have been generated to support the implementation of continuous manufacturing for pharmaceuticals. As a result, common concepts, and themes, relevant to continuous manufacturing from a pharmaceutical perspective have started to emerge. Key aspects of continuous manufacturing, including batch definition, control strategy elements, and process validation/verification, have been identified and discussed between industry and regulators. The next section outlines progress made since 2014, based on the presentations, discussions, and comments received during the 2016 ISCMP, as well as other published papers on continuous manufacturing.[9,10]

Common Concepts

In a continuous manufacturing process, the input material(s) are continuously fed into and transformed within the process, and the processed output materials are continuously removed from the system. This description can be applied to an individual unit operation or the entire manufacturing process consisting of a series of unit operations. Although the amount of material being processed at any given instance may be relatively small in a continuous manufacturing process, the process can run over a period of time to generate desired quantities of finished material with the necessary quality.

There are different approaches for the integration of continuous manufacturing unit operations. In an *end-to-end approach*, the drug substance and drug product process steps are fully integrated into a single continuous process, in which there is no isolated drug substance or intermediate. Most pharmaceutical companies though are currently developing a *hybrid approach*, in which continuous manufacturing steps may be incorporated for portions of a drug substance or drug product process, or for an entire drug substance or drug product process. The 2016 ISCMP presentations illustrated many examples of the hybrid approach. The most common ones being continuous drug synthesis processes, continuous granulation, and continuous direct compression processes for solid oral drug products. However, 2 examples were presented for full end-to-end continuous manufacturing processes without the isolation of the API. In some cases, this approach may not be selected as in the scenario where multiple dosage forms are manufactured using the same API.

To ensure that products with the desired quality are being consistently manufactured over time, a continuous manufacturing process needs to operate under a *state of control*. In practice, a continuous manufacturing process does not run at a steady state condition, but rather at the condition in which a set of critical

process parameters and quality attributes are kept within a specified range of target values (state of control). Deviations from these target values triggered by *disturbances* do generally occur during the normal operation but they can be detected and are often small enough to be negligible or controllable, resulting in no or minimal impact on product quality. Larger changes in process variables and quality attributes may happen when the continuous manufacturing process is in a *transient state*, such as during start-up, shut down, changes from one operating condition to another, and significant disturbances (e.g., equipment failure or sudden change in raw material attributes). Understanding of the process sensitivity against disturbances can be a useful tool to elucidate the remaining risk on product quality that should be addressed by the appropriate control strategy.

For a continuous manufacturing process, understanding *process dynamics* of how a material flows through the process is important with respect to the *material traceability* (the ability to preserve and access the identity and attribute of a material throughout the system) and performance of the unit operation and the integrated system. The understanding of process dynamics is obtained by the characterization of *residence time distribution* (RTD) for individual unit operations and the integrated system. RTD is a probability distribution that describes the amount of time a mass or fluid element remains in a system or process. Its shape depends on several factors such as operating conditions (e.g., flow rates), material properties, and equipment design. The width of RTD for a particular system (i.e., a single unit operation or an integrated system comprising of several unit operations) reflects the degree of *axial dispersion* or *back mixing* within that system, which has impact on the propagation of disturbances and material traceability. The *characteristic time* is an important measure of the system dynamics for an integrated continuous manufacturing process. It can be used to determine how long a change or disturbance will propagate through and leave the system, how long the system will take to transition to a new operating condition, or which segment of materials will be affected by the change.

Another relevant characteristic of the continuous process is the kinetic profile of the process over time from a material flow perspective (e.g., the thermal profile or the energy dissipation over time profile). If known, this information provides a powerful understanding of the transformation and the material properties that the process can produce. Together with the RTD, the kinetic profile describes the complete trajectory of the process that the material in transit follows. In practice, the RTDs should be determined, but the kinetic profiles may not be easily obtainable.

Quality Risk Management

The regulatory expectation for assurance of product quality is the same for batch and continuous manufacturing. The risks associated with continuous manufacturing processes, however, can be different from batch manufacturing processes due to certain unique characteristics of continuous manufacturing processes, such as potential exposure to transient disturbances as described above. Therefore, the quality risk management of continuous manufacturing warrants special considerations.

Risk Assessment

Characterizing process dynamics in relation to material properties, equipment design, and process conditions is fundamental to understanding potential risks of continuous manufacturing to product quality, largely because of their potential impact on material traceability and disturbance generation and propagation. Such characterization and understanding can be adequately achieved during pharmaceutical development based on the QbD approach, and need to be obtained at the system level in addition to the unit operation level due to the integrated nature of the process. Information generated in the risk assessment aids development and regulatory evaluation of a control strategy proposed for a continuous manufacturing process design.

Risk Control

A control strategy for continuous manufacturing can include a combination of different elements and will be described subsequently.[11] An enhanced control strategy is required to ensure a continued state of control throughout the entire operation and collection of materials. Continuous manufacturing offers an opportunity for utilizing real-time data. The real-time data, when properly aggregated, can provide instantaneous confirmation on the state or "health" of a continuous manufacturing process and help to ensure an appropriate level of risk control. The use of these data for process monitoring and control lends itself to RTRT to maximize the benefit of continuous manufacturing, although the RTRT is not a regulatory requirement for continuous manufacturing.

Risk Communication

Development and routine production using continuous manufacturing processes can generate a substantial amount of data. Such a data-rich environment unquestionably leads to enhanced product and process understanding and constitutes a foundation of effective risk communication. From both industry and regulatory perspectives, these data need to be analyzed, utilized, and communicated appropriately to link elements of the proposed control strategy with specific risks to product quality, enable real-time quality decisions (e.g., batch release) during commercial manufacture, and aid continual improvement of the process (e.g., improving process efficiency and reducing process variability).

Batch Definition

There is a consensus that the following definitions of a batch and lot with specific references to the US Code of Federal Regulations 21 CFR 210.3 are applicable to continuous manufacturing.

- Batch means a specific quantity of a drug or other material that is intended to have uniform character and quality within specified limits and is produced according to a single manufacturing order due the same cycle of manufacturer.[12]
- Lot means a batch, or a specific identified portion of a batch, having uniform character and quality within specified limits; or, in the case of a drug product produced by continuous process, it is a specific identified amount produced in a unit of time or quantity in a manner that assures its having uniform character and quality within specified limits.[12]

In Japan, the definition of a lot is provided by Ministry of Health, Labour and Welfare Ministerial Ordinance No.179 (2004). Although there is no definition of a batch, it would be possible to grasp the meaning of a batch in the United States as the same as a lot in Japan.

- "Lot" throughout this Ministerial Ordinance means a grouping of the products or raw materials that are manufactured so as to have a uniform quality in a series of the manufacturing process for a certain manufacturing period.[13]

The regulatory definitions are associated with the amount of material produced and not the mode of manufacture, type of equipment, or source of raw materials. Therefore, it is possible for a

continuous manufacturing process to make a batch according to the above definitions.

Batch definition for continuous processes is critical to material traceability and has implications for product recalls and other potential regulatory actions. With the appropriate control strategy and the continued state of control, it could be possible to designate large quantities of product to be of uniform character and quality, even though different batches of incoming/raw materials or processing conditions (e.g., manipulated variables for an active process control such as feedback control) may have been utilized during the production run. In this context, a batch can be defined based on the production time period, quantity of material processed, equipment capability, or production variation (e.g., different batches of in-coming materials), and also can be flexible to meet variable market demands by leveraging the advantage of operating continuously over different periods of time. From a regulatory perspective, it is expected that the size of batch is established prior to initiation of each production run.

Control Strategy

According to ICH Q8(R2) and Q10, the control strategy is a planned set of controls, derived from current product and process understanding that ensures process and product quality.[11,14] The controls can include parameters and attributes related to drug substance or drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control. For continuous manufacturing processes, the control strategy places special emphasis on controlling the quality of the material or product in response to potential variations in the process and equipment conditions, properties of incoming raw materials, or external environment factors over time. Therefore, it can ensure the continued state of control operation, proper product collection, and batch release. The needs for process monitoring to ensure a continued state of control operation and segregate non-conforming materials during continuous operation, as well as the integrated nature of the system, increase the need for enhanced control strategies by utilizing control elements other than the traditional off-line end product testing. According to Lee et al.,[10] the control strategy implementation can be categorized into 3 levels based on the robustness, flexibility, and complexity of control elements and will depend on many factors, including desired product performance, manufacturing process, and process dynamic characteristics (e.g., product heterogeneity and mixing patterns). In practice, the control strategy can display a combination of control elements at all 3 levels, if the quality risk is properly controlled and mitigated. The following discussion highlights some key aspects related to control elements specific to the control strategy for continuous manufacturing.

Material Traceability

Tracking incoming raw and intermediate materials to the final product throughout the process is essential for understanding material and disturbance propagation, as well as determining product collection and rejection. As an integrated continuous manufacturing process lacks a discrete, physical separation of materials inherent in a batch manufacturing, traceability for continuous manufacturing processes is based on probability or RTDs. There are 3 approaches to address this important aspect:

- *First principle model approach* is built on mechanistic understanding and quantitative modeling of the thermodynamic and kinetic behavior of a system. As such, it requires a wealth of knowledge about the underlying chemical and physicochemical principles (e.g., quantitative nucleation and growth kinetics in the case of crystallization or reaction constants of main and associated side reactions in the case of chemical transformations). To ensure a valid prediction capability of the first principle model, the key mechanistic factors need to be understood and a sufficient predictive power of the model needs to be demonstrated under transient conditions. This model approach emphasizes the understanding of at least the dominant mechanistic factors determining the overall process dynamics, and it allows the prediction of the process dynamics and certain quality attributes simultaneously (e.g., purities over time for chemical reactions). However, it may not be obtainable for many processes, especially for complex systems.
- *Empirical model approach* focuses on the empirical approximations that model the process kinetics in a generalized way. The empirical model approach is only targeted for the prediction of process dynamics based on experimental determination at the macroscopic level. The advantage is that the same set of empirical equations may be widely capable of describing the process dynamics of a whole variety of process units by feeding numerically different parameters into the system. They are universally achievable for most if not all unit operations. The other benefit is that the real-time solutions of such equations can be computed on the process control system with relatively fast response times. The disadvantage is that the model validity may be in narrower operating condition ranges compared to the first principle model approach. However, if developed properly, the model validity should be wide enough for most, if not all, real-world operating conditions.
- *Model-free approach* eliminates all underlying model equations and describes the process dynamics in the form of a lookup table like a “train schedule.” This approach can be adapted to all process steps and can be performed on the process control system. Therefore, it could serve as a practical tool to describe the process dynamics of known processes. However, the model-free approach does not allow a priori simulations of unknown setups.

When developed and used properly, any of these approaches can provide adequate information on the RTD and inform where a particular material segment is in the process at any given time. However, from a practical standpoint, empirical model or model-free approaches are easier to develop, implement, and operate but are constrained by the experimental ranges used to develop them. For the purpose of diverting non-conforming materials, there are several key scientific considerations for these 3 approaches. First, the approach needs to be validated through experimentation, for example, for their capability to trace the identified non-conforming material segment through the system to the rejection point(s) under conditions reflecting routine commercial production. Second, the conditions in which the approach can be applied to adequately monitor material traceability need to be understood and defined. Third, maintenance, including updates to the approach, is necessary, for example, when the new variability (e.g., materials with new properties) or operating conditions, which were not considered in the original set of conditions and data used to develop and validate the model approach, is introduced to the process.

Control of Raw Materials

Continuous manufacturing may require additional control of raw material attributes in comparison to typical batch processes. Evaluation of material attributes (e.g., particle size distribution and

density of the API and excipients) in relation to their impact on the flow properties within the given equipment or system is important. The knowledge gained from such studies aids the development of a robust continuous manufacturing process in an open-loop setting (i.e., without any active control) and leads to a better understanding of the system capability in handling batch-to-batch variability during the continuous operation from a quality assurance standpoint. This information could help set appropriate specification for incoming raw materials, and such learning can be further enhanced throughout the product lifecycle for continual process improvement. For legacy products that are to be switched from batch to continuous manufacturing, the existing specifications for the API and excipients may need to be re-evaluated for its use in a particular continuous manufacturing process design.

Process Monitoring and Control

For continuous manufacturing, real-time monitoring of quality attributes of raw or in-process materials may employ a combination of process parameter trending, spectroscopic and chemometric PAT tools, and non-spectroscopic and soft sensor sources of process analytical data. A combination of process monitoring approaches can be used to monitor the state of the process, allow detectability of transient disturbances, and enable other key facets of the control strategy critical to continuous operation such as advanced process control, material diversion systems, and RTRT.

Sampling frequency, or rate, is a critical aspect of process monitoring and control. It should depend on the process dynamics and should be "fit for purpose." In general, sampling frequency can be classified into the following 3 categories according to its intended use:

- Category 1: The sampling frequency should be sufficiently high to measure the fastest dynamics or detect the most rapid changes (e.g., a transient disturbance with a large magnitude and short duration or a sudden step change) expected to be encountered within the integrated system during production. The key here is to determine the maximum rate of change for the process and align the frequency of measurements with that rate, so no process change outside the acceptable range will be missed. This type of high sampling frequency may be utilized to gain process understanding during pharmaceutical development, demonstrate the continued state of control operation (e.g., during process development, process validation, and commercial production when the high process capability has not been fully demonstrated), or monitor fast dynamic responses during changes in the operating condition (e.g., changes in the flow rate or raw material attributes).
- Category 2: The sampling should be frequent enough to detect a process drift and enable a sufficient number of measurements for a trend analysis. This type of sampling frequency may be suitable for monitoring system start-up and shutdown to determine when the system reaches a state of control and therefore when quality material can be collected. The sampling frequency here depends on the process dynamics during these transient states and can be lower than those for Category 1 in cases where the system has a long characteristic time (e.g., slow chemical reaction kinetics). It may also be used for trend analyses during the process verification stage, where lower frequencies may be justified once the high process capability is demonstrated.
- Category 3: The sampling frequency should be established to be able to adequately assess the quality of a batch based on sound statistical criteria. As described above, because of the need for higher sampling frequencies to monitor process dynamics, continuous manufacturing processes may involve sampling plans that generate and use significant larger amounts of data (i.e., *large n* sampling plans) than traditional plans. Such large *n* sampling plans can be used to support the RTRT.

In general, the development of a sampling strategy within the control strategy of continuous manufacturing processes needs to consider all the above categories. Most importantly, sampling frequencies used at each control points (e.g., process parameters, in-process controls, or end product testing), collectively, should be sufficient for their use in managing planned changes, responding to disturbances, ensuring continued state of control operation, and therefore assuring that desired product quality is consistently met. This categorization approach may lead to single or multiple layers of control if warranted by the risks.

By utilizing on-line and at-line measurements at sufficient sampling frequencies for monitoring and controlling quality attributes, continuous manufacturing provides an opportunity for using a performance-based approach to demonstrate quality. In this approach, product quality is demonstrated and assured by showing conformance to the specification at relevant control points (e.g., in-process controls of quality attributes) in the process. This performance-based approach can provide effective regulatory oversight and, at the same time, the needed operational flexibility desired by industry to manage and improve the process within its quality management system (continual improvement as outlined in ICH Q10).[11] To utilize this approach, final product critical quality attributes need to be fully identified and their link to control points in the process needs to be clearly established.

Material Collection and Diversion

A continuous manufacturing process and its control strategy are designed to maintain a state of control and minimize the risk of producing non-conforming material. However, there could be temporary disturbances over the entire production run, where it becomes necessary to isolate the material segments affected by these disturbances from the main portion of materials produced in the same run. The amount of material that needs to be isolated and diverted to the designated diversion point depends on the severity (i.e., magnitude and duration) of a disturbance and the mixing characteristics (e.g., the degree of back mixing or axial mixing) of the system. The ability to divert the non-conforming materials during a continuous production run relies on the methods and frequency of process monitoring and control, as well as knowledge on the mixing pattern of the system and its RTD.

In addition, during the planned start-up and shut down, there could be a period of time when the in-process materials do not meet the acceptance criteria for quality attributes. Appropriate criteria should be established based on the control strategy to ensure that the product collection occurs only when the continuous manufacturing process is in a state of control and the requisite product quality is achieved.

Real-Time Release Testing

RTRT is the ability to evaluate and ensure the quality of in-process materials and final product based on process data that typically include a valid combination of measured raw material attributes and process controls. In this context, the RTRT implementation of continuous manufacturing processes necessitates the establishment of clear relationships between final product critical quality attributes and control elements incorporated into the process (e.g., controls of quality attributes of raw and in-process materials, controls of process parameters, or their combinations). An

example includes the RTRT approach for dissolution, which is based on the real-time measurements of in-process material quality attributes (e.g., drug concentration, tablet hardness, weight, and particle size distribution) and utilization of an appropriate dissolution model to use these measured quality attributes to predict the tablet dissolution performance.

The RTRT approach warrants careful consideration of the sampling strategy. The selected sample size needs to be representative of the batch and justified statistically to provide an adequate confidence level and coverage. Due to the high frequency of data collection, appropriate statistical methods for large sample size should be applied to increase the confidence level that the batch conforms to the desired quality. In the case of PAT equipment failure, established alternative procedures can be used for process monitoring and batch release. These procedures could include end-product testing or using surrogate measurements to ensure that products maintain an acceptable level of quality.

Data Processing and Management

The integrated nature of a continuous manufacturing process and its control strategy requires a robust computer-aided platform to supervise the production. The key elements of control strategy, such as process monitoring and control that often include on-line PAT, diversion of non-conforming materials, and RTRT, can be integrated into the computer-aided automation system to facilitate effective real-time process monitoring, decision making, and follow-up action. The design, validation, and qualification of such a system with equipment warrant the following considerations. The system should be designed to process a large amount of data during the production run and reconcile different sources of data for intended purposes (e.g., supporting RTRT). Validation should focus on system requirements determined by the process dynamics and control strategy. Qualification should demonstrate the functionality of the system under normal operating conditions and in response to planned disturbances or common failure modes.

Process Validation/Verification

Existing guidances and standards can be consulted for process validation and when applicable, continuous process verification. For example, the concept of aligning process validation activities with a product life cycle activities described in the FDA Guidance to Industry: Process Validation: General Principles and Practices, the EMA Guidelines for Process Validation,[15] and the Enforcement Notification of GMP Ministerial Ordinance[16] (Pharmaceutical and Food Safety Bureau/Compliance and Narcotics Division Notification No. 0830-1 (2013)) is relevant to continuous manufacturing. Within this conceptual framework, continuous manufacturing has advantages over batch manufacturing in the following aspects. Continuous manufacturing can generate a data-rich environment in fewer trial or production runs by using PAT tools for process development and monitoring. It can also utilize the same or highly similar equipment for pharmaceutical development and commercial production. These unique features naturally support or facilitate early execution of process validation activities and process improvement. They also make continuous process verification well suited to the evaluation of continuous manufacturing processes by utilizing data from production batches to validate the process and demonstrate processing in accordance with the total system design concept. Therefore, continuous process verification approach essentially supports validation with each manufacturing batch, replacing a conventional process validation approach (e.g., 3-batch validation at set point) that has been used historically.

Conclusion and Future Opportunities

Following the 2016 ISCMP, common themes regarding continuous manufacturing, as highlighted above, have started to emerge based on the increasing knowledge and practical experience gained by and shared among industry and regulators. The support from regulatory agencies (noticeably from the FDA, EMA, and PMDA), industry, and academia have made the shift from the batch to continuous manufacturing process possible. Although significant progress has been made, there are still plenty of opportunities to further encourage and advance continuous processing in pharmaceutical manufacturing.

As a result of globalization, pharmaceutical manufacturers may supply drug products to various countries from a single manufacturing facility, subjecting the process and facility to the jurisdiction of numerous regulatory authorities. In this context, the need to obtain multiple regulatory approvals for continuous manufacturing may hinder manufacturers from implementing continuous manufacturing technology. Potential delays in obtaining regulatory approval globally may impact the business case for this emerging technology or delay the supply of new therapeutics to patients in emerging markets. For this reason, there is a need for international harmonization of approaches for expediting the global adoption of continuous manufacturing. One potential mechanism to promote a better alignment of regulatory approaches for evaluating continuous manufacturing is to establish common guidelines in this topic through effective collaboration among relevant stakeholders under the ICH.

Throughout the symposium discussions, the need for a globally harmonized guideline on continuous manufacturing became evident. There was a consensus among symposium attendees that clear expectations of scientific and regulatory approaches for continuous manufacturing will lower perceived regulatory barriers and encourage implementation. A future ICH guideline can use experience gained to date, build on current ICH guidelines, including ICH Q8, 9, 10, and 11, and provide clarity on relevant regulatory and GMP expectations. The scope of a proposed ICH guideline should elaborate on scientific and regulatory issues outlined in this paper and the 2014 ISCMP regulatory White Paper.[1]

There is an unparalleled opportunity for manufacturers, in collaboration among one another or with academia, to build a knowledge base in continuous manufacturing as part of the knowledge management system. This knowledge, when developed and organized properly, may serve as a foundation for developing standardized continuous manufacturing equipment and computer-aided control systems that can be used to build a flexible modular manufacturing platform for a wide range of small- or large-molecule products. A platform like this would not only streamline process development, but also would better facilitate regulatory assessment of the technology through standardization. There is currently a lack of enabling manufacturing and testing technologies which allow effective integration of the upstream and downstream processes to support the end-to-end manufacturing of commercial products and RTRT for biological molecules (e.g., mAbs). Therefore, opportunities exist to address these deficiencies through research and development.

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