REVIEW ARTICLE

Modernizing Pharmaceutical Manufacturing: from Batch to Continuous Production

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Abstract The Food and Drug Administration (FDA) regulates pharmaceutical drug products to ensure a continuous supply of high-quality drugs in the USA. Continuous processing has a great deal of potential to address issues of agility, flexibility, cost, and robustness in the development of pharmaceutical manufacturing processes. Over the past decade, there have been significant advancements in science and engineering to support the implementation of continuous pharmaceutical manufacturing. These investments along with the adoption of the quality-by-design (QbD) paradigm for pharmaceutical development and the advancement of process analytical technology (PAT) for designing, analyzing, and controlling manufacturing have progressed the scientific and regulatory readiness for continuous manufacturing. The FDA supports the implementation of continuous manufacturing using science- and risk-based approaches.

Keywords Continuous processing · Quality by design · Process analytical technology · Control strategy · Traceability

Introduction

The Food and Drug Administration (FDA) regulates pharmaceutical drug products to ensure a continuous supply of high quality drugs in the USA. In regulating the pharmaceutical manufacturing sector, the vision for FDA's Pharmaceutical Quality for the 21st Century Initiative is to promote a maximally efficient, agile, flexible pharmaceutical sector that reliably produces high-quality drugs without extensive regulatory oversight [1]. The pharmaceutical manufacturing sector is in transition, but overall processes, which are largely batch in nature, remain relatively inefficient and less understood as compared with those in other chemical process industries [2].

The lack of agility, flexibility, and robustness in the pharmaceutical manufacturing sector poses a potential public health threat as failures within manufacturing facilities that result in poor product quality can lead to drug shortages [3]. Drug shortages are a critical health care issue, affecting individual patients across the USA. Recognizing that shortages commonly begin with a supply disruption related to product or facility quality, FDA is focusing on encouraging and sustaining advancements in pharmaceutical manufacturing. Continuous manufacturing is one such innovation that has a great deal of potential to improve agility, flexibility, and robustness in the manufacture of pharmaceuticals. This article summarizes the potential advantages of continuous manufacturing for pharmaceutical products and highlights some unique quality aspects for consideration and how they may be addressed.

Definitions of Batch and Continuous Manufacturing

General definitions of batch and continuous process are described below [4].

(1) *Batch process.* The raw material(s) is charged into the system at the beginning of the process, and the product is discharged all at once sometimes later. No ingredients cross the system boundaries between the time the raw material(s) is charged and the time the product is discharged (Fig. 1a).

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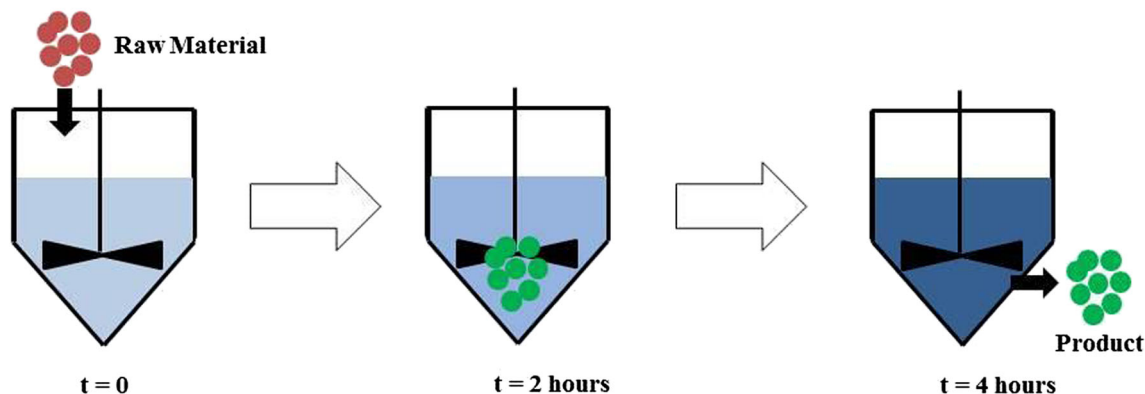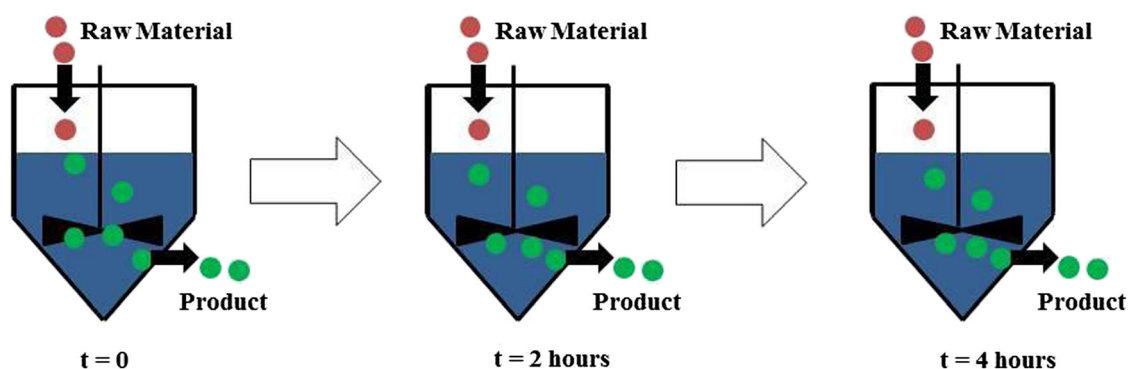
Fig. 1 A simple depiction of two types of manufacturing. **a** Batch manufacturing: the material(s) is charged before the start of processing and the product is discharged at the end of processing. **b** Continuous manufacturing: material(s) and the product are simultaneously charged and discharged from the process, respectively

(2) *Continuous process.* The material(s) and product are continuously charged into and discharged from the system, respectively, throughout the duration of the process (Fig. 1b).

The above definitions can be applied to individual unit operations or an entire manufacturing process consisting of a series of unit operations. A pharmaceutical manufacturing process often consists of a combination of batch and continuous unit operations [5]. As such, there are situations where certain unit operations can be considered "continuous" (e.g., tablet press or roller compaction) while the manufacturing process as a whole can be considered "batch." These situations are outside the scope of this article. Figure 2 depicts an example of the future vision for continuous pharmaceutical manufacturing in where (1) individual continuous unit operations are connected to form an integrated manufacturing process, (2) process analytical technology (PAT) systems are utilized to provide real-time data for process monitoring and control, and (3) engineering process control systems are implemented to mitigate the impact of raw material and process variability on the quality of finished products.

Batch manufacturing is traditionally utilized for the production of pharmaceutical products. In this type of process, materials from one step are usually tested off-line as per the in-process controls and stored before they are sent to the next processing step. If the in-process material does not meet quality expectations, it may be discarded or, under certain circumstances, reprocessed prior to moving to the next process step [6].

In continuous manufacturing, materials produced during each process step are sent directly and continuously to the next step for further processing. Each processing step needs to reliably produce an intermediate material or product with acceptable characteristics. Extending processing time of particular unit operation(s) (e.g., synthesis, crystallization, blending drying, etc.) to achieve the desired quality may not be possible for continuous manufacturing as it may create disruption for downstream unit operations. Continuous manufacturing, compared to batch manufacturing, thus often involves a higher level of process design to ensure adequate process control and product quality.

Fig. 2 A conceptual fully integrated continuous manufacturing process. A typical batch manufacturing process for tablets is also presented for comparison
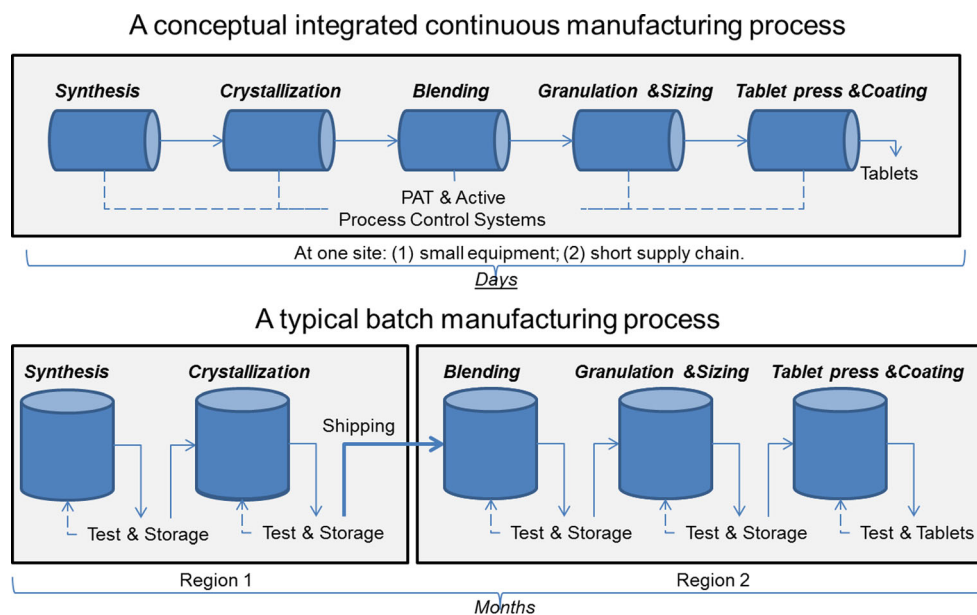
Development and Manufacturing Opportunities

Compared to traditional batch manufacturing, continuous manufacturing provides several potential opportunities to improve control of product quality and to increase flexibility of manufacturing. Examples are provided below.

The pharmaceutical industry currently has a limited ability to rapidly increase production in the face of drug shortages or other emergencies such as pandemics. Bringing up a new facility or manufacturing line in response to such emergencies may take up to several months or years. Continuous manufacturing can potentially permit increasing production volume without the current bottlenecks related to scale-up, providing more response capacity. Scale-up options, such as operating the process for longer periods of time, utilizing parallel processing lines, or increasing the flow rate through the process, can be built into the process design and verification. Additionally, due to the small volume of materials needed to run continuous manufacturing systems, it may be possible to design and optimize a continuous system on commercial scale equipment, thus eliminating scale-up [5, 7]. Eliminating scale-up bottlenecks in the path to market may increase the agility to facilitate rapid clinical development of breakthrough drugs.

Due to economic factors, supply chains for many active pharmaceutical ingredients (APIs) and final drug products span several countries and contain multiple supply vulnerabilities. Under current batch manufacturing process steps, intermediates may not be immediately processed. Instead, they are stored in containers and shipped around the world to the next manufacturing facility. Continuous manufacturing provides advantages to shorten supply chains. Continuous manufacturing allows the production at various scales with a given process, which may facilitate regional or in-country manufacturing.

Under a continuous operating mode, hold times between steps can be eliminated. This is a significant advantage for APIs or intermediates that can degrade over time or are sensitive to environmental conditions, directly improving the overall drug product quality. Furthermore, the small scale of continuous manufacturing can decrease the safety hazards associated with highly energetic or hazardous materials and potentially allow for more flexibility in the use of non-specialized manufacturing facilities [8].

Continuous manufacturing is strongly aligned with the FDA's support of the quality-by-design (QbD) paradigm for pharmaceutical development. QbD is a systematic scientific and risk-based approach to pharmaceutical development. This approach advises companies to demonstrate product and process understanding and to use this understanding to implement effective quality control strategies to achieve a predefined objective. The ICH Q8(R2) (Pharmaceutical Development); ICH Q9 (Quality Risk Management); ICH Q10 (Pharmaceutical Quality System); the ICH Q1WG on Q8, Q9, Q10, and Question and Answers; the ICH Q8/Q9/Q10 Points to Consider document; and the ICH Q11 (Development and Manufacture of Drug Substances) documents have been issued and provide high-level guidelines with respect to the scope and definition of QbD as it applies to the pharmaceutical industry [9–14]. Development of a robust process relies on utilizing the acquired product and process understanding to identify sources of variation to product quality and to design appropriate control strategies to address these risk areas. Continuous manufacturing provides an opportunity to utilize this enhanced product and process understanding to adopt advanced manufacturing controls to produce uniformly high-quality products with reduced waste resulting from the generation of out-of-specification material [2].

Continuous unit operations are generally more efficient than their batch counterparts and offer much higher throughput per unit volume and per unit time, thereby often greatly reducing the size of the processing equipment. The manufacturing footprint is further reduced because the material flows from one processing step to the next and does not need isolated suites or dedicated modules. For this reason, a substantial reduction in both capital and operating expenses for a continuous process can be achieved [15]. Furthermore, continuous processing can decrease the amount of potentially expensive API required for process development studies, greatly reducing the materials cost of process development and optimization efforts. However, initial investment is required for the construction of facilities and the generation of process knowledge required for continuous manufacturing. The current inventory of available batch manufacturing facilities can be an economic barrier for the adoption of continuous manufacturing [16]. Therefore, potential candidates for adoption of continuous manufacturing at present are likely new therapeutic entities or approved drugs with a very large market requiring the new or expansion of existing manufacturing facilities.

Continuous manufacturing may facilitate the streamlining of the manufacturing process through the removal of corrective or work-up unit operations. One potential example is reaction telescoping (collapsing of a multistep process into a smaller number of steps or unit operations). Traditional batch reactions normally include several reaction steps with isolation and purification work-up operations in between each reaction step. The post-reaction work-up steps can be highly time consuming and generate large volumes of waste. To avoid this lengthy process, telescoping could be an ideal alternative and well suited for continuous flow chemistry [17]. Other examples include (1) the potential to eliminate downstream corrective drug product unit operations, such as sizing steps (e.g., granulation, milling) due to better control of the particle size distribution during crystallization and (2) reduction in the segregation risk from continuous blending [18, 19]. Continuous manufacturing may also facilitate the adoption of emerging processing technologies which are well suited for continuous operations [20]. Examples of the potential advantages of continuous manufacturing for the development and operation of pharmaceutical processes are presented in Table 1.

Challenges do exist in the implementation of continuous manufacturing. In continuous manufacturing, materials continuously flow between unit operations and product is formed continuously over a long period of time. Considerations unique to continuous production should be evaluated when developing a control strategy for a continuous process as the process, product, or environmental conditions could potentially vary over time. These considerations, for example, include accounting for material attributes that affect flowability,

Table 1 Features and potential benefits of continuous manufacturing

Features of continuous manufacturing	Benefits
Small equipment and space required	Efficient, high throughput per unit volume and per unit time Reduced safety hazards
Short supply chains	No storage/shipping costs for intermediates Fast response to market shortage Less degradation for sensitive intermediates
All key characteristics should be roughly constant at any time	Lower batch-to-batch variations Simple to develop process monitoring systems and control strategies Possible eliminations of some downstream corrective steps
Non-stop continuous transport of materials from unit to unit (no batch handling)	Reduction of number of operators on site Increased operator safety
Continuous flow production	Easy scale-up, such as a longer running time Potential for reaction telescoping Facilitation of new synthetic routes (e.g., microwave, photochemistry, ultra-high or low temperature) Safe operation of highly exothermic reactions

understanding the impact of process dynamics on quality including process startups and shutdowns, and designing appropriate measurement systems for process monitoring and control [5, 20]. Fundamentally, the design, control, and optimization of continuous manufacturing facilities require a systems approach [21]. Regulators and industry will need to continue to develop knowledge and experience with such systems-based methods to support a broader implementation of continuous pharmaceutical manufacturing.

Quality Considerations for Continuous Manufacturing

Process Understanding

Design of experiments (DOE) has become a common tool to increase process understanding for the process ranges of interest. The fast response of a continuous process to changes in process parameters allows for gathering a large amount of experimental information in a short time from smaller quantities of product. Moreover, continuous processing, compared with batch processing, offers a greater opportunity to develop and better utilize process models to gain process knowledge, since their governing equations generally can be simplified. Predictive process models can be used as a simulation tool to supplement experiments throughout process development and thus enhance process understanding. For example, process modeling can be utilized to perform sensitivity analysis to identify the key interactions or relationships among process

parameters and material or product attributes in support of a quality risk assessment. In addition, predictive process models can be used to develop and assess control strategies for continuous processes [22–24].

For continuous manufacturing, understanding the dynamics of how a material flows through the process is critical with respect to material traceability (the ability to preserve and access the identity and attributes of the material throughout the process). Such an understanding of process dynamics can be obtained by characterization of residence time distribution (RTD) through a tracer experiment and/or process modeling [25–27]. The RTD is a probability distribution that describes the amount of time a mass or fluid element remains in a process. The RTD curve can be utilized to predict the propagation of material or disturbances through the system or, in a retrospective analysis, to determine when the ingredients in a given product unit were fed to the manufacturing system. The RTD is dependent upon several factors such as processing time, equipment parameters, and material properties. One option to describe the material traveling through the system is to define a traceability resource unit (TRU) [28]. A TRU can be specified as a segment of material that flows through the process together and can then serve as a unique identifier from a process history perspective to achieve traceability throughout the integrated continuous process. Material traceability has implications on control strategy described below.

If the manufacturing process is integrated with the packaging process, unique package identifiers (e.g., serial codes, timestamps, etc.) can further link product supply chain traceability to process traceability (e.g., TRU). In this manner, a packaged product for marketing can be traced from raw materials to processing conditions and all the way to the distribution to the end customer.

Batch Definition for Continuous Processes

The definition of a batch has regulatory implications, particularly with respect to current good manufacturing practices (cGMPs), product recalls, and other regulatory decisions. Current cGMP regulations describe a "batch" as a specific quantity of 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 during the same cycle of manufacture [29]. Furthermore, for continuous processing, a "lot" is defined synonymous to "batch" (or specific identified portion of a batch) and is a specific identified amount produced in a unit of time or quantity in a manner that assure its having uniform character and quality within specified limits. Note that the regulatory definition of "batch" is related to an amount of material and not the mode of manufacture. Consequently, it is possible for a continuous manufacturing process to generate batches.

In a continuous process, it is important to link material traceability to the definition of a batch. If continued *state of control* operation (see below for its definition) is demonstrated, it could be possible to designate large quantities of product to be of uniform quality, even though different batches of raw materials and/or different processing conditions may have been utilized during the production run. Within this framework, a batch can be defined based on the production time period, quantity of material processed, equipment run time capability, or production variation (e.g., different lots of incoming raw material). The batch definition for continuous manufacturing is therefore closely linked to the design of the control strategy for the process, which should be constructed to ensure uniform quality within a batch.

Control Strategy

The control strategy for a continuous process should be designed to control the quality of the product in response to potential variations in the process, equipment conditions, incoming raw materials, or environmental factors over time. Control strategy implementations generally can be categorized into three levels described below.

Level-1 control utilizes an active process control system to monitor the quality attributes of materials in real-time. Process parameters are automatically adjusted in response to disturbances to ensure that the quality attributes consistently conform to the established acceptance criteria. This level of control represents a high degree of product and process understanding as the design of an engineering control system entails expressing the dynamic relationships among process parameters, raw material, and product attributes in a quantitative and predictive manner. The risk of producing out-of-specification product is lowered through the implementation of adaptive engineering controls which can enable a real-time release strategy.

Level-2 control consists of pharmaceutical control with appropriate end-product testing and flexible raw material attributes and process parameters within the established design space (the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality) [30]. The product and process understanding obtained through the establishment of a multivariate design space facilitates the identification of potential sources of raw material and process variability that can impact product quality. Understanding the impact that variability from these sources has on in-process materials, downstream processing, and drug product quality provides an opportunity to shift controls upstream and to reduce the reliance on end-product testing [9].

Level-3 control relies on tightly constrained material attributes and process parameters. There may be limited understanding on how raw material and process variability affects

product quality. The risk of releasing poor-quality product is lowered through extensive end-product testing. Level-3 control is generally not feasible for many continuous manufacturing process designs, in part because of the risk of potential transient process disturbances. The characteristic mixing patterns of many continuous manufacturing systems promote the adoption of level-1 control, although a hybrid approach combing the different levels of control is viable for some continuous manufacturing process designs [31].

State of Control

State of control is a condition in which a set of controls consistently provides assurance of continued process performance and product quality [11]. A continuous process operating under a state of control helps to ensure that product with the desired quality is being consistently manufactured. A state of control could differ from "steady state" where all the parameters and material attributes associated with the process do not vary with time. Criteria for the establishment of a state of control depend upon the control strategy employed.

For a level-1 control strategy, process parameters are designated as a manipulated variable or a controlled variable. Quality attributes of in-process materials may also be candidates for a controlled variable. Manipulated variables are automatically varied in response to disturbances to maintain the controlled variables at their set points or within the target range. Variations in these parameters would not necessarily represent a departure from a state of control. A state of control is then established by real-time monitoring the controlled variables. The active process control system for integrated processes should be able to appropriately respond to both fast (within a unit operation) and slow (propagating from upstream unit operations) disturbances [24, 32].

If a level-2 control strategy is utilized, raw material attributes and process parameters may vary within the established design space without impacting the desired product quality. A state of control can be established by real-time monitoring of the raw material attributes and process parameters to ensure that they remain within the established design space. At this level of control, end-product testing or surrogate models are primarily utilized for a confirmatory purpose.

When the process parameters reach and can be maintained very closely to their target values in conjunction with tight control of raw material attributes, a level-3 state of control is achieved. As mentioned above in level-3 control, the relationships among raw material and process variability and product quality might not be well characterized and understood. For this reason, process monitoring needs to be supplemented with end-product testing at an appropriate frequency to ensure that the process is being maintained in a state of control. While a level-3 control strategy may be feasible for a well-mixed, segregation-resistant continuous manufacturing system, it is unlikely to be operationally feasible for a continuous process with low back-mixing or for high-risk formulations (i.e., low drug content products). Although a high degree of back-mixing may promote process robustness, it may represent a physical limitation to material traceability [33]. Thus, integrated continuous manufacturing systems naturally lead to the development of a pharmaceutical control (level 2) or engineering control (level 1) strategy to ensure that quality product is being consistently manufactured.

Diversion of Non-conforming Material

The ability to isolate and reject material that is out of specification if the process is no longer in a state of control is one of the key aspects of a continuous manufacturing control strategy. During planned startup and shutdown, there may be periods of time when the in-process material or product does not meet the target quality attributes. During these periods, procedures to isolate the non-conforming material should be initiated. In addition, during normal operation, although the continuous process will typically maintain a state of control, there may be temporary process disturbances or upsets over the course of a production run. If the disturbance cannot be mitigated by the process, it is important to remove the impacted material. The extent of material to be isolated and rejected depends on the duration, frequency, and severity of the disturbance and the mixing patterns of the system.

Diverting a portion of the in-process material or product relies on the capability to detect and isolate out-of-specification material at some point in the process. Physical separation of non-conforming material can occur immediately at the point of the detected failure or downstream if justified by knowledge of the residence time distribution to trace the non-conforming material through the process to the diversion point. As the impacted material travels downstream through the process, back-mixing may occur and disperse the impacted material to adjacent material. From a material traceability perspective, this means that the impacted material as well as adjacent (prior and subsequent) material portions should be tracked and isolated as necessary. Predictive models, including but not necessarily limited to RTD models, can be extremely useful for determining the amount of adjacent material that requires diversion.

Establishing a priori criteria for product collection, product rejection, rejection of an entire batch, and indicating how or who makes those decisions is important for continuous manufacturing process from a quality management perspective, given that disposition decisions may need to be made in real time. The establishment of adequate process monitoring criteria (e.g., alarms, adjust limits, and isolation limits) can prevent ad hoc decisions and helps to ensure the desired quality and consistency of a final product. Consideration of the disposition strategy of product obtained when process is not

under control (e.g., during startup, shutdown, and process upsets) is also an important component to assure quality during the manufacturing run.

Implementation of Process Analytical Technology

PAT is a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of quality attributes of raw and in-process materials and process conditions, with the goal of ensuring final product quality [34]. Due to the absence of isolated intermediates and the typically faster process dynamics for a continuous process that may necessitate more frequent measurements, real-time monitoring of process parameters and quality attributes of in-process materials typically constitutes an essential component of a control strategy for the establishment of a state of control. In addition to supporting the validation and control of the manufacture process, PAT tools and principles can be used to gain process understanding. Multivariate models are often used for extracting process knowledge (e.g., blend uniformity) from the data provided by process analyzers (e.g., spectroscopic measurements). Consensus standards are available for building, validating, and maintaining such multivariate models [35–37].

The sampling interface for continuous manufacturing systems can be challenging. Industrial experience indicates that poor measurement performance is often attributable to sampling system issues rather than the process analyzer itself [38]. On-line and in-line measurements may reduce but do not necessarily eliminate sampling errors [39]. Thus, sampling considerations should be assessed. For example, the location of the sensor should be evaluated to achieve representative sampling and minimizing the effect of the probe on the process. Powders and dispersions limit the penetration depth of spectroscopic techniques. This may increase the importance of the sample probe location [40], size of the sampling spot, intensity of the incident signal, etc. The sample size for the measurement should be representative of a unit dose and consider factors such as flow rate, penetration depth, and the number of scans. It is important to utilize the knowledge of the process dynamics (e.g., RTD) for determining the adequate sampling frequency for PAT measurements. The measurement frequency implemented should provide sufficient resolution for the detection of a pulse of variability from a process disturbance.

The utilization of PAT tools can be applied to measuring surrogates for the quality attributes of a final product, some of which may have already been incorporated into the control strategy for process monitoring and control. For this reason, continuous manufacturing naturally lends itself to real-time release testing (RTRT), which is the ability to evaluate and ensure the quality of in-process materials and/or final product based on process data that typically include a valid combination of measured raw material attributes and process controls

[9]. A supervisory control and data acquisition (SCADA) system can be implemented that incorporates measurements of process parameters, incoming raw material, and in-process material attributes, as well as final product quality attributes with a model of the process dynamics to reconcile the data in order to support RTRT [32, 41]. Due to a high frequency of data collection, statistical methods for large sample sizes can be applied to increase the confidence level that the batch conforms to the desired quality [42]. RTRT batch calculations should consider the observed variance in critical quality attributes over the production run to account for intra batch variability. A risk analysis aids in consideration of PAT failure, and procedures can be developed in order to establish contingencies for process monitoring and batch release. The procedures could include end-product testing or utilizing surrogate measurements to ensure that the product maintains an acceptable level of quality [5].

In addition to naturally lending itself to RTRT, the increase in the amount of process and quality data collected during a continuous production facilitates the adoption of multivariate process monitoring approaches. Multivariate statistical process control (MSPC) is a process monitoring approach used to determine whether the variability in the process is stable over time [43]. It can be used to detect abnormal events in the process that may lead to adverse consequences (e.g., out-of-specification product, equipment malfunction, or process safety incident) if not mitigated and provide diagnostic information of which process variables may be responsible for the event. Taking advantage of the fact that process variables are often correlated, MSPC simplifies process monitoring by reducing the number of control charts being tracked without losing information. MSPC may also enhance the detection of abnormal process operations by identifying changes in the relationships among process parameters and quality attributes [43] that may be difficult to detect using solely univariate process monitoring approaches [44].

Conclusions

Continuous pharmaceutical manufacturing offers potential flexibility, quality, and economic advantages over batch processing, both in process development and manufacturing for the pharmaceutical sector. Over the past decade, there have been significant advancements in science and engineering to support the implementation of continuous pharmaceutical manufacturing. These investments along with the adoption of the QbD paradigm for pharmaceutical development and the advancement of PAT for designing, analyzing, and controlling manufacturing have progressed the scientific and regulatory readiness for continuous manufacturing. Building on this progress, research efforts should continue in several key areas including the development of integrated process models

similar to the approaches utilized by the chemical industry; the development of a database of excipient properties to capture the behavior of common raw materials within different processing environments, the standardization of processing equipment integration components to increase flexibility; and the advancement of automatic process control systems (e.g., model predictive control). Collaborative research efforts should leverage expertise in academia, industry, and regulatory bodies. The knowledge and experience gained from such collaborative science and research activities will help manufacturers to more efficiently and effectively address the quality considerations discussed in this article and to ensure that the application of regulatory policies reflect state-of-the-art manufacturing science.

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