Current Recommendations for Implementing and Developing Continuous Manufacturing of Solid Dosage Drug Products in Pharmaceutical Manufacturing

Contents

1. INTRODUCTION AND SCOPE

This document is developed in response to an FDA invitation to prepare and submit a proposal for an industry coordinated best practices document in Continuous Manufacturing, issued by Dr. Janet Woodcock during the workshop on "the Future of Pharmaceutical Manufacturing" held at Rutgers University on May 7, 2015.

This document, which has been drafted by C-SOPS regulatory working group involving 22 volunteers from 16 companies, and which incorporates input from RCPE and CMAC member companies, attempts to capture the current scientific and regulatory understanding of the best available methodologies for selecting, specifying, implementing, controlling, and optimizing continuous drug product manufacturing systems for solid oral dosages from the group assembled in response to the above invitation. This document is not intended to be prescriptive, and individuals looking to implement the technology described herein are encouraged to engage regulatory agencies (FDA/EMA) early in their adoption process as mentioned in the *Draft Advancement of Emerging Technology Applications to Modernize the Pharmaceutical Manufacturing Base Guidance for Industry*[1].

The focus of this document is on U.S. FDA, innovator and generic drug product manufacturers, and solid oral dosage forms only.

2. KEY ASPECTS OF CONTINUOUS SOLID DOSE MANUFACTURING

2.1. Fundamental Engineering Concepts and Definitions in Pharmaceutical Solid Dose Continuous Manufacturing

To achieve a working understanding able to support the sound design and efficient implementation, any manufacturing process should be investigated at three scales – system scale, unit operation scale, and bulk material scale. This is certainly true of any continuous manufacturing process, which is a system with multiple, highly integrated unit operations operating synchronically and at the same rate. To design, optimize, and control such systems, it is often important to study, define, and model the system as well as its unit operations. Optimization and distributed control should be considered at the system level, as the optimum conditions of each individual unit operation do not lead to optimum, or sometimes even feasible, performance of the integrated system.

The basis of any manufacturing process is the unit operation. A **unit operation** is defined as a basic step in a process. The goal of the unit operations is to impart a physical or chemical change to the incoming material needed to eventually transform them into a completed product. Transformations can include mixing, agglomeration, milling, coating, consolidation, separation, crystallization, evaporation, filtration, or chemical reactions.

Unit operations can be classified into one of three categories: batch, semi-continuous (semi-batch) and continuous. Unit operations are sorted into these categories based on how materials

enter and leave the process. Batch operations involve sequentially loading a set amount of material, processing that mass, and then discharging all of the transformed material. **Continuous operations,** on the other hand, involve material constantly being loaded, processed, and unloaded without interruption. **Semi-continuous operations** have elements of both batch and continuous in that materials are either constantly loaded or constantly removed from the process, but not without interruption.

In order to manufacture product of proven quality, all unit operations need to be in a **state of control**. A state of control can be defined as a condition in which a set of controls consistently provides assurance of continued process performance and quality. [6]
Unlike batch or semi- continuous unit operations, continuous unit operations can be designed to be run under, or near, a subset of state of control known as a steady state condition. Generally speaking, a **steady state condition** is defined as a process state in which the IPCs, CPPs and / or quality attributes are kept approximately constant, or the rate of change with respect to time of those variables is approximately equal to zero over a relevant time span. In commercial practice, changes do occur, but deviations from the steady state are small enough to either be negligible, or to be controllable. A continuous system where the output variables are maintained within a desired range is in a **dynamic state of control**.

The time invariant nature of continuous, steady state processes, and the near-time-invariant nature of continuous systems in a dynamic state of control, leads to important advantages over their time variant batch counterparts. Most of those advantages stem from the fact that when something changes (either a process parameter change due to an equipment change, a material change due to variation in incoming materials, or an environmental change affecting the process) the change can be detected.

When a change happens and the system goes through a dynamic period (varying with time), such a period is known as a **transient state**. Batch and Semi-continuous unit operations are always in a transient state and a deeper process knowledge is required to know if the process is following the normal trajectory. Therefore, it is easier to demonstrate a state of control (whether static or dynamic) for a steady state process than that of an intrinsically time variant process. This does not rule out transient states in either steady state or non-steady state process as being proven to being under a state of control.

Within continuous manufacturing, the amount of time material takes to move through the process is usually critical to the performance of the unit operation and the controllability of the system as a whole. Within a steady state unit operation, the **mean residence time** is defined by the amount of material contained within the unit operation (often called holdup or residence mass) divided by the rate at which material is entering/exiting the system. The mean residence time can be thought of as the average amount of processing time the unit operation works to perform its physical or chemical transformation on the material.

If all material entering the unit operation spends the same amount of time within the unit operation then this is called a **plug flow** system. Within a plug flow system all the material has the same amount of residence time which is equivalent to the mean residence time. Plug flow systems do not apply any mixing to the material along its flow directions, and are unable to

eliminate any fluctuations entering the system. In reality all systems have some variation in residence time of the materials traveling through the system. The system is considered to be "more plug flow" as the variation in the residence time becomes small compared to the total time it stays within the system.

In contrast to a plug flow system, a continuous stirred tank reactor (CSTR) system is one in which ideally the incoming components are instantly mixed with all materials residing in the unit operation the instant they enter the unit operation. In CSTRs materials spend a highly variable time within the process. In theory, any segment of material entering the unit operation has a real, although small, chance of exiting the tank instantly or staying within the tank forever. As with the ideal plug flow concept, an ideal CSTR mixed system is an abstraction, but one that can be used to closely approximate the behavior of many well mixed systems.

As material enters a system the distribution of possible residence times associated with any one segment entering the tank is known as the **Residence Time Distribution** (RTD). For any particular unit operation, the RTD describes both the distribution of possible times an elementary unit of the material will remain within the system, and the fraction of material that spends specific amounts of time in the system.

If a continuous solid oral dosage pharmaceutical manufacturing system was a perfect plug flow system, then it would have a RTD resembling a delta function, and variability or **noise** would propagate straight through the system and lead to content variability over time (inter-location variability) of the end products content uniformity. In order to counter this feeding noise, the process can be intentionally designed to have a wider RTD. If this wider RTD is designed correctly, it will blend the feeder variability back to the average value. This is sometime referred to as the degree of **back mixing** within a system. The width of the RTD can be used to calculate the back mixing (dispersion) coefficient of the system.

As the RTD is directly tied to the mixing capability of the unit operation, it is often discussed in context of single unit operations. However, the RTDs from sequential unit operations can be combined to create a system RTD, representing the distribution of residence times from a given entrance to the exit of the entire system, which may potentially be used as part of an active control strategy. When joining multiple continuous operations together to form a system, the amount of time it takes for a transient state to propagate through the line becomes the important metric. This is known as the **characteristic time**. The characteristic time can be used to predict how long it will take for a transient state or change to the process to leave the system, how long it would take the system to transition to a new steady state, and which product units will be affected by the transient state.

2.2. Key Difference to Common Pharmaceutical Concepts and Definitions of Continuous over Batch

This section presents and initial discussion on key topics which, while addressed in other places within this document, deserved a high level overview because the differences in how these are applied to batch processing versus continuous processing may vary to a large extent.

2.2.1. Process Analytical Technology (PAT)

Since the release of the FDA's Guidance for Industry PAT – A framework for innovative pharmaceutical development, manufacturing and quality assurance [2], increased emphasis has been placed on the utilization of tools for obtaining in-process data. Most often PAT has referred to spectroscopic/chemometric tools that most typically monitor only the API within the formulation. This has been applied to batch solid dose applications such as blend uniformity measurements. These tools are useful in advanced pharmaceutical manufacturing applications and primary means of obtaining chemically specific (API) information, though they currently require significant chemometric model maintenance in commercial practice which has the potential to hinder utilization.

Continuous manufacturing introduces additional opportunities for the usage of spectroscopic/chemometric PAT tools as well as significant non-spectroscopic and **soft sensor** sources of process analytical data. As defined in the FDA's Guidance for Industry PAT – A framework for innovative pharmaceutical development, manufacturing and quality assurance, PAT to be a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality. It is important to note that the term *analytical* in PAT is viewed broadly to include chemical, physical, microbiological, mathematical, and risk analysis conducted in an integrated manner"[2]. The integrated nature of continuous manufacturing systems enables significant increases in the number of approaches and data sources that fit the definition of PAT as compared to batch solid dose manufacturing. PAT as it pertains to continuous manufacturing includes significant non-spectroscopic or soft sensor sources of process analytical data useful for process monitoring and control. While not chemically specific, non-spectroscopic process data can, in many instances, be acquired and analyzed on a faster time scale, while simultaneously being more robust and more easily interpreted than spectroscopic data. Moreover, when properly aggregated with other data, non- spectroscopic information can provide a broader, more complete characterization of the state of the system.

2.2.2. Defining Batches for Continuous Processes

The fundamental concept of a batch from 21CFR210.3 is the same whether the product is produced via batch or continuous processing. "*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 during the same cycle of manufacture"[3].

Defining a batch for a continuous manufacturing process has more options than in an batch manufacturing process as there are a number of regulatory acceptable approaches.[4]. Flexibility in batch size from run to run is an important advantage of continuous processing, enabling each batch size to vary to support Just in Time and Make to Order supply chain strategies. The batch size for any individual run may be specified before the start of that run.

The amount of material subject to a quality disposition decision could be defined as:

- All of the material discharged from the process between two specific times (irrespective of the amount of material produced).
- A specific quantity of material produced (irrespective of the time taken).
- All of the material produced between two specific process events (for example, specific process conditions).
- All of the material that is "intended" to contain a specific lot or quantity of a specified input material.
- Plus other scenarios as justified by the applicant (e.g., the quantity of product made from a single tote of drug substance, or x kg/h)

It may be possible for a continuous process to be operated with no pre-defined maximum run-time, in which quantities of product are defined during the operation of the process in a flexible way, based on principles of science and risk (for example, as any entity produced in a certain time, or containing a certain lot of a starting material), and subjected to a disposition decision [5]. These decisions would need to be made prior to the beginning of any manufacturing run, but would provide increased flexibility for changing market demands.

Based on the definition of batch, a continuous process batch size will not be bound by the 10 times size of the pilot/biobatch rule [27], as the more relevant parameter is flow rate, typically kg/h, rather than kg per lot, as long as run time concerns such as material build-up, generation of heat, etc. are sufficiently evaluated and risks mitigated, and is evaluated during the Validation Lifecycle[8] as controlled by the applicant's Quality System

The batch size may be registered as a single value, a proven acceptable range (e.g. minimum and maximum size), or as design space including two or more parameters (e.g. rate and time). Movement within the PAR or design space would not be considered a change. Movement outside of the range later in product lifecycle is possible as more experience and data becomes available. Notification of regulatory agencies would follow same guidelines for CPPs, PARs, NORs, or design spaces, depending on how the batch size definition is classified.

For post-approval changes, the reduction of batch size should not require as much information as extending the run time, as concerns such as material build-up, generation of heat, etc. would be less significant for shorter runs. However, shorter run times may impact the sampling plan and total amount of data generated.

Risk assessments conducted to determine the impact that a change in batch size/duration can have on the quality of the product should be leveraged to justify the reporting category. Extensive monitoring resulting from in-process controls provides a high level of confidence in the quality of the product. Demonstrating that product quality is acceptable for the extended batch size/run time should provide justification for future use.

The process validation strategy contained within the Quality System should outline the boundaries of the validated process based on the definition in the regulatory filing and the means to establish evidence that the continuous process is capable of consistently delivering quality

product. The length of a campaign may be flexible and non-prescriptive depending on the chosen batch definition. The duration of the batch may not matter as long as a state of control for the process is maintained. The maximum length of time over which the process is run may be determined by monitoring specific product attributes or process parameters rather than by validating a single fixed length of run time or range.

2.2.3. In-Process Monitoring and Control

According to ICH Q10, a **control strategy** is a planned set of controls, derived from current product and process understanding, that ensures process performance and product quality. The controls can include parameters and attributes related to drug substance and 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.[6].

The integrated nature of continuous manufacturing systems enables increased opportunity for the utilization of in-process monitoring and control. In-process control may take on a larger role in continuous processes as compared to batch processes as there is no pause between unit operations and therefore an automated in-process measurement, control, and action plan is desirous from efficiency and ease of regulatory compliance standpoint.

The control strategy for a continuous solid dose pharmaceutical manufacturing process may 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 of varying sophistication and robustness / flexibility. See Sau L. Lee et al.[7]. In practice a control strategy may exhibit elements of all three of these levels. In all cases the quality risks must be mitigated and controlled.

The use of a specific manufacturing configuration, composed of specific processing equipment, operating within the ranges required to ensure that acceptable product is manufactured, and the optional use of a sensing and closed loop control configuration designed to maintain the product in a suitable dynamic state of control, may constitute elements of established conditions[28], to the extent that the state of process understanding at the time of FDA approval indicate that such conditions are deemed necessary to ensure acceptable product quality. Changes to specific values of processing parameters within the established operational ranges do not constitute changes to established conditions, as they are intrinsic requirements of implementing a closed loop control strategy.

2.2.4. Data Storage and Handling

Continuous manufacturing systems will create significantly more data than their batch manufacturing counterparts. This presents both opportunities and challenges from an operational standpoint. Increased data access allows for greater use of statistical determination which may allow for more representative sampling and reporting. Though, with this increased amount of

data, decisions must be made during the design and qualification as to what information is part of an internal record-keeping/reporting system and for what duration recorded data must be saved and in what form. With large amounts of data, there will be spurious data points, and this must be understood and handled in the proper statistically supported manner.

2.2.5. Process Modeling

Continuous manufacturing systems are more amenable to modeling than their batch counterparts. Models seek to predict the output attribute(s) from a unit operation as a function of incoming material properties and process parameters. Models can predict steady state output, or, more usefully, the dynamic response of a unit operation to changes in incoming materials or processing conditions. Such models can also be used to predict the fate of transient states in material properties, process parameters, etc.

Models of individual unit operations can be combined into "flowsheet" models of multiple unit operations, or even entire manufacturing systems, including the effect of local and distributed control systems. Such integrated models are in fact useful to design, tune, and optimize control systems.

Such models, once properly verified by comparison to experimental data, can be used to examine the robustness of the system with respect to transient states, either individually or in combination. Strategies for dealing with perturbations, as enabled by models, could include the implementation of control strategies that mitigate the effects of transient states on product quality, and the use of models to predict when faulty product should be excluded from the output stream.

A model that has been experimentally verified can be used advantageously as part of a company's strategy for establishing robustness and reliability of the manufacturing system.

3. PRODUCT COLLECTION, SAMPLING OF CONTINOUS SOLID ORAL DOSE MANUFACTURING PROCESSES

3.1. Strategies for Product Testing and Release

3.1.1. Acceptance Criteria

In general, the acceptance criteria for critical quality attributes (CQAs) of drug product manufactured using a continuous system may not necessarily differ from the criteria used for batch processes unless special circumstances warrant the need. As with conventional batch processes, different criteria may be established for process verification and routine release with continuous manufacturing. The Process Qualification (Stage 2) criteria should provide a high level of assurance that the relevant specification or compendia criteria could be met prior to commercial manufacture as outlined in the FDA Guidance for Industry Process Validation:

General Principles and Practices [8]. Due to the different goals to be achieved during process validation, there may be differences in the sampling plan during Continued Process Verification (Stage 3) and routine release.

3.1.2. Sampling Plan Considerations for Product Testing and Release with Continuous Manufacturing

For uniformity tests (e.g., content uniformity), the goal of any sampling plan should be to ensure that the release data is representative, insuring the uniformity of the material under disposition. While the sampling plan for product release testing is an important element in ensuring that the batch is of an acceptably uniform character, other elements may also be available with continuous manufacturing to assure that the batch is of an acceptably uniform character (e.g., analysis of data from process parameter monitoring, in-process material attributes monitoring using spectroscopic or non-spectroscopic techniques).

It should be acceptable to use different sampling plans for Stage 1 (Process Design), Stage 2 (Process Qualification), and Stage 3 (Continued Process Verification) as the goals of the testing at the different stages will vary. Sampling plans could consider material and process risk assessments as well as process dynamics, process understanding and process capability. Sampling plans for early clinical trial material production may be different from the later stages of production, depending on process understanding and availability of on-line/at-line PAT models (including spectroscopic and non-spectroscopic sensor data).

The sampling plan for a continuous solid dose manufacturing process should outline the frequency of sampling and the amount of samples to be taken and/or tested from each given sample point. The data gathered from the sampling plan will be evaluated against the pre-specified acceptance criteria. It may be acceptable for the sampling plan frequency/stratification to be based on a time or volume basis.

When applicable, sampling plans that generate and use significantly larger (i.e., 10x) amounts of data than traditional plans ("large n" plans) might require different statistical criteria than traditional plans. Such large n plans are able to detect faulty product with a larger degree of statistical confidence. Thus, such plans might allow for larger RSD criteria, since the estimates of the standard deviation contain less uncertainty. Conversely, large n plans create a larger probability of detecting single values outside any given interval than traditional plans, not because the product is of inferior quality, but because they collect more samples. Thus, it is imperative for large n sampling plans to be based entirely on criteria for the mean and the standard deviation (i.e., interval of confidence criteria) without requiring an absolute interval.[25,26] Though, it should be noted, that an absolute interval (for example 75-125%) can also be implemented to augment the control strategy to prevent extremely low or high drug content in the dosage unit.

3.1.3. Real Time Release Testing Considerations

Real Time Release Testing (RTRT) is "the ability to evaluate and ensure the quality of in-process and/or final product based on process data, which typically include a valid combination of measured material attributes and process controls" [9].

While implementing an RTRT approach is not required for continuous manufacturing, the development of suitable drug products using the Quality by Design approach is achieved more effectively and efficiently using continuous processes. Typically, the ability to make multiple and rapid process changes across interconnected unit-operations allows for easy implementation of designed experiments with a more efficient use of material compared to batch processes. In addition, continuous processing methodology allows for real time generation of experimental samples (tablets) from a DOE for use in PAT method calibration and validation. The resultant knowledge gained from rich data sets can lead to greater process understanding of design spaces and critical process parameter (CPP)interactions which are more amenable to RTRT approaches, either through the development of predictive CQA models or in combination with direct on-line/at-line measurement of material intermediate attributes or CQA's. For example: NIR for tablet or blend API concentrations linked to automated tablet weight(s) measurements for real time analysis of identity, content uniformity and assay.

It should be added that some in-process controls (IPC) may not be part of RTRT; however, the performance of non-RTRT IPC's may need to be considered from a risk assessment perspective as mitigation for operational deviations or downtime of RTRT controls (e.g. NIR maintenance).

3.2. Approaches for Product Collection/Segregation of Non-conforming Materials

With continuous manufacturing, the ability to divert potentially unacceptable product from the final collection stream becomes enabled with advanced monitoring and control. This is intimately related to the use of spectroscopic or non-spectroscopic PAT (potentially with RTRT) as well as control strategies, and procedures that describe when to collect and when to divert product may be established during Stage 2 Process Qualification, prior to Stage 3 Continued Process Verification.

When appropriate, procedures to handle out-of-trend (not out-of-specification) product may be considered, along with associated offline sampling strategies, during Stage 2 Process Qualification as well. In addition, consideration for collection criteria in response to process upsets in the middle of production should be defined. Depending on the severity of the process upsets and the understanding of dispersion/residence time distribution in the continuous manufacturing unit, such process upsets may lead to an increased sampling/testing plan to assure product quality. However, if the process upset is severe enough (magnitude and/or duration) such that it will be expected to lead to product that is non-conforming to the collection criteria, that subset of the batch in question may be segregated and/or rejected.

The evaluation of overall residence time distribution and the understanding of propagation of a transient state between extraction points in the system are important to justify the amount of material at risk due to an unexpected event or transient state.

While product collection criteria at startup/shutdown may refer to product potency and/or uniformity with continuous manufacturing, it may be expected that the approach followed at start of product collection be similar to the already established approaches for tablet press startup procedures with batch manufacturing (the tablet press operation is continuous, by design). The control strategy may propose and justify the product collection criteria, which may be built upon actual at-line/on-line measurements of CQAs or surrogate measurements of CQAs in question, or may be built upon appropriate equipment design and process understanding/process modeling.

4. EXISTING GUIDANCE AND STANDARDS APPLIED TO SOLID DOSE CONTINUOUS MANUFACTURING

Despite significant differences, many elements of existing guidance documents written for batch process can be relevant for continuous manufacturing processes.

ASTM E2968-14, Standard Guide for Application of Continuous Processing in the Pharmaceutical Industry contains comprehensive information for elements of continuous manufacturing. This document is perhaps the most recent, concise and relevant information on pharmaceutical continuous manufacturing. It covers both primary upstream API drug substance manufacturing as well as secondary downstream drug product. While the scope of ASTM E2968-14 is broader than solid dose continuous manufacturing, applicable covered topics include: quality decisions, operator intervention, diversion of nonconforming material, residence time, time distribution, and traceability, process time constraints, sampling and data collection, process control systems and robustness, robustness of instruments and analyzers, parameter screening, process validation and verification, cleaning, and system specification (different than batch systems)[10]. While some of these topics have also been covered within this document, here we specify applicability to pharmaceutical continuous manufacturing of solid dosage forms.

ASTM E2587 – Standard Practice for Use of Control Charts in Statistical Process Control contains extremely useful guidance on the application of control charts to help in interpretation of steady state data.

ASTM E2281 – Standard Practice for Process and Measurement Capability indices contains guidance on how to assess the performance of a process relative to appropriate limits to calculate risk and inform downstream control strategy choices.

Applicable FDA guidance documents include:
PAT – (1) A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance,
(2) BA and BE Studies for Orally Administered Drug Products – General Considerations,
(3) Process Validation: General Principles and Practices, and
(4)Drug Product Chemistry, Manufacturing, and Controls Information.
These have been referred to in other sections of this document as appropriate.

Aspects of many of the ICH Quality guidance documents are also applicable to continuous manufacturing, **as the baseline quality standards remain the same**, regardless of the type of

manufacturing process. All Q3B to Q3D [11-13] should be applicable to continuous manufacturing processes. Risk assessment approach to Q3D may need to take into account any potential for time dependent increases in elemental impurities during drug product processing. Products must comply with the requirements stated in ICH Q6A Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products Chemical Substances[14]. Periodic or skip testing, parametric release and in-process tests sections may be allowed for continuous manufacturing processes. Use of monitoring of in-process attributes in lieu of end product testing should be facilitated by continuous manufacturing.

ICH Q8(R2) [9] Pharmaceutical Development is written at a level that allows it to be applied to continuous manufacturing processes. It emphasizes a science and risk-based holistic approach to achieve enhanced product and process understanding and control strategy. ICH Q8(R2) also mentions advanced control systems and modeling, and regulatory flexibility (Design Space). The extensive process monitoring/feedback systems that may be used for continuous manufacturing have the potential to implement control strategies that are less parameter based and more continuous quality monitoring based. It is important that the reliance on process parameter control does not impede the implementation of these alternative control strategy approaches.

The risk assessment approaches defined in ICH Q9[15] can be directly applied to continuous manufacturing. The greater complexity of continuous manufacturing processes and control strategies (more potential variables that can impact product quality) could increase the size of risk assessments. ICH Q10[6] (Pharmaceutical Quality System) is also applicable to continuous manufacturing, though it may require modification to accommodate advanced control strategies and the large volumes of data generated by continuous manufacturing systems.

Other ASTM Standards that contain elements which may be applied to continuous processing include E2363 Terminology Relating to Process Analytical Technology in the Pharmaceutical Industry[16], E2475 Guide for Process Understanding Related to Pharmaceutical Manufacture and Control[17], E2537 Guide for Application of Continuous Quality Verification to Pharmaceutical and Biopharmaceutical Manufacturing[18], E2898 Guide for Risk-Based Validation of Analytical Methods for PAT Applications[19].

Stability

ICH Q1A(R2) Stability Testing of New Drug Substances and Products applies to continuous manufacturing processes [20]. However, defining the number and size of primary stability batches may not be consistent with the recommended approach contained in this document. For example, the batch size for continuous processing should be flexible. As such, what would $1/10^{th}$ scale imply? One-tenth of the longest run time or quantity? Also, the information gained from a single long batch during which there may be multiple start-ups and shut-downs, as well as heat generation and residual material buildup, may or may not be superior to that obtained from three small scale ($1/10^{th}$) batches.

Elements of other ICH stability guidance documents: ICH Q1B Stability Testing: Photostability Testing of New Drug Substances and Products[21]; ICH Q1C Stability Testing for New Dosage Forms Annex to the ICH Harmonized Tripartite Guideline on Stability Testing for New Drugs and Products[22]; ICH Q1D Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products Requirements[23]; and ICH Q1E Evaluation of Stability Data are also applicable to continuous manufacturing [24].

5. APPLICATION OF CONTINUOUS MANUFACTURING THROUGHOUT THE PRODUCT LIFECYCLE

5.1. New Chemical Entities - IND

Continuous manufacturing can be used for development of new drugs, including the manufacture of clinical supplies. The amount of information contained in the IND will be less and not as comprehensive as that contained in an NDA. As the drug progresses from Phase 1 to Phase 3 developments and additional process knowledge is gained, subsequent updates to the IND will contain more detailed information. Process knowledge, controls, and acceptance criteria for both IPCs and release testing should be stage appropriate. Expectations of the level of readiness/ verification of the in-process models (e.g. NIR for blend) should be tempered for the manufacture of Phase 2 and 3 clinical supplies, as the chemometrics will likely be developed in concert with the formulation and manufacturing process. Although PAT information may be collected, batch release will likely be via traditional sampling and analytical procedures, until the modern analytical methods are validated and process models can be developed for material traceability etc. cGMPs would apply to all stages for the application of continuous manufacturing.

5.2. New Chemical Entities – NDA

The requirements for filing batch and continuous manufacturing processes are fundamentally the same. The differences lie in the way those requirements are met.

One of the first activities conducted during Process Validation Stage 1: Process Design[8], regardless of whether a batch or continuous manufacturing process is developed, is to create a Quality Target Product Profile (QTPP) for the drug product, which defines the performance characteristics and properties that the dosage form must possess. Risk assessments are performed to identify potential process parameters that may impact CQAs listed on the QTPP. Experiments are conducted and CPPs and CQAs are identified (including operating ranges and acceptance criteria for in-process/release tests). Alternatively, the relationship between a quality attribute and process parameters is identified and an appropriate control loop is developed to maintain that quality attribute. RTRT methods are in the process of being developed, and may not be suitable for batch release during Stage 1. As such, batch release will often be via traditional sampling and off line testing. The formulation and process knowledge obtained during Stage 1 is used to define the control strategy, which is used to identify the commercial manufacturing process and controls to be used during Stage 2.

Stage 2: Process Qualification, is to evaluate the process designed during Stage 1 and determine if it is capable of reproducible commercial manufacture. RTRT methods may or may not be sufficiently developed at this point for use in batch release.

Once the Stage 2: Process Qualification is demonstrated, the product progresses to the final stage of validation, Stage 3: Continued Process Verification.

5.2.1. Module 3.2.P Drug Product

Module 3.2.P Drug Product lists the required information that must be included in the drug product sections of an NDA. Although originally written for batch processes, most of the information and concepts stated in the CTD are also applicable to continuous manufacturing processes. As such, continuous drug product manufacturing processes can be filed using the existing CTD format (with minor adjustments) when writing Module 3.2.P Drug Product. The following provides a high level assessment of each section contained in Module 3.2.P.

Section 3.2.P.1 should be applicable to drug product continuous manufacturing process with little (if any) adjustments. For excipients that can be purchased in multiple grades, the specific grade of the excipient may be listed in the composition table.

Section 3.2.P.2.1, Components of Drug Product, should be applicable to continuously manufactured solid dose drug product processes with little (if any) adjustments. It contains information about the drug substance (3.2.P.2.1.1 Drug Substance) and excipients (3.2.P.2.1.2 Excipients). In addition to the information that is typically provided for drug substance and excipients used for batch processes, any specific material attributes for the drug substance and excipients that are required to allow continuous processing may be described in these sections.

Section 3.2.P.2.2.1, Formulation Development should be applicable to drug product continuous manufacturing process with little adjustment as well. Due to the fact that continuous manufacturing processes might depend differently on material properties than batch manufacturing processes, this section may focus on how certain grades of excipients were selected to ensure manufacturability. It is a good practice to have appropriate material attribute characterization as part of the development section. Changes to the formulation over the course of development, leading up to the commercial formulation, may be discussed. Discussion of the selection and justification of the components selected for the dosage forms, and Critical Material Attributes (CMAs) for the drug substance or excipients, and how they may impact the manufacturability, performance or stability may be applicable to continuously manufactured solid dose drug product processes. If the continuous manufacturing process is replacing a batch process, bioavailability and bioequivalence may need to be demonstrated for the batch and continuous manufacturing processes. The definition of a Batch Size can be achieve using any of the concepts discussed in section 2.2.2 or other approaches that meet the intent of relevant regulations and laws. Flexible batch sizes should be allowed. Definition of a lot (portion of a batch) may also be required, especially for sectioning off portions of extremely long runs.

The purpose of this section 3.2.P.2.3, Manufacturing Process Development, remains the same for the both batch and continuous manufacturing processes: present the process development data

that demonstrates the process is robust, controlled and capable of producing product that is safe and effective. Some areas where continuous manufacturing may differ include:

- Acceptable ranges for process parameter operating ranges may also need to address residence time, back mixing
- State of Control – when is it met; how do you ensure the process maintains it; what happens if the process drifts out of control (diversion; how to detect it and how much/between what points).
- IPCs/Distributed Control System (DCS) – PAT may be used with IPCs/DCS; feedback/feedforward, model development and maintenance; sampling interval and how that relates to the residence time and back mixing.
- Scale up – longer running time, different mass throughput, or different size equipment
- Models – discussion of process models and chemometric models which are not used for release.

Section 3.2.P.2.5 Microbiological Attributes, should be applicable to continuous manufacturing processes as is. Cleaning procedures and the frequency of cleaning should be defined in the PQS.

Section 3.2.P.3.2, Batch Formula, will need to be adjusted for continuous manufacturing processes. Although the dosage unit formulation for a continuous manufacturing process may not be different than that for batch processes, the batch size (and therefore batch formula) will be different for continuous manufacturing processes. Furthermore, the batch size may be expressed as a function of rate (e.g., 40 kg/h) rather than mass (e.g., 400 kg). Flexibility in the batch size may be allowed, with justification. This section may link into the one that defines a batch and lot.

3.2.P.3.3, Description of Manufacturing Process and Process Controls, serves the same purpose as its batch process counterpart, although it will be adjusted to accommodate continuous manufacturing processing, equipment and monitoring. It may include a flow chart with the sequential manufacturing steps and the IPCs implemented at each step. For level 2 and 3 control strategies, operating ranges (NORs, PARs, Design Space) for CPPs and PARs for non-critical process parameters should be defined. [7] For level 1 control strategies, the section may alternatively describe targets and ranges for the quality attributes and which process parameters are manipulated to control those attributes. This could be in lieu of traditional CPP / PAR approaches. The manufacturing description will include operating parameters for different equipment (e.g., loss in weight feeders) as well as models used to define design space.

Process Validation and/or Evaluation, 3.2.P.3.5, could be conducted in accordance with the January 2011 FDA Guidance for Industry, Process Validation: General Principles and Practices [8]. All three stages of validation identified in this guidance document (Stage 1: Process Design; Stage 2: Process Qualification; Stage 3: Continued Process Verification) can be applied to the development and commercialization of drug product continuous manufacturing processes. Though, it should be recognized that a continuous process is running in a state of control when acceptable material is being produced, unlike traditional batch processing where each batch is

evolving in time. For this reason, the process is being continuously verified at (or near) steady state.

Control of excipients, section 3.2.P.4 is applicable to drug product continuous manufacturing processes. Increased characterization of excipient properties may be necessary to ensure they possess material attributes that are necessary for continuous manufacturing processes, falling within the defined design space. Necessary grades and material attributes that go beyond pharmacopeia monographs, and their control, may be discussed in this section.

Drug Product release specifications (3.2.P.5.1) are required for product made by either batch or continuous manufacturing processes. Differences between batch and continuous manufacturing may be in the testing approaches and acceptance criteria that may be used to demonstrate compliance with those specifications. Because the level of monitoring/sampling/analysis will likely be much greater for continuous manufacturing processes, this enhanced process monitoring and control with continuous manufacturing facilitates the use of RTRt and/or large n methods in lieu of traditional sampling and analytical techniques for end product testing. RTRt may utilize information that is collected using statistically based sampling plans and acceptance criteria (including large n acceptance criteria). Meeting such criteria would assure compliance, if tested, with the test listed on the specification (for example, USP <905> Uniformity of Dosage Units).

Section 3.2.P.5.2, Analytical Procedures, is applicable to drug product continuous manufacturing processes, although the focus of it may shift from lab analytical techniques (e.g., HPLC) to online methods (e.g., NIR). If lab analytical techniques are used for off-line IPC and release testing, then this section should not change much. However, if PAT approaches are used for batch release, then the content of this section will resemble those written for products utilizing RTRt. Chemometric models used for release would be included in this section. The amount of information contained in this section for model calibration, validation, and maintenance included in this section has to be balanced with information provided in the PQS. In other words, how much of that information needs to be in the CTD versus how much can be handled under the PQS.

Validation of Analytical Procedures, section 3.2.P.5.3 is applicable to drug product continuous manufacturing processes and is meant to ensure the analytical procedures are reproducible, robust, accurate, etc.. Current guidance documents and approaches used for currently implemented PAT procedures could be used as an example for this section.

Section 3.2.P.5.4 Batch Analyses, is applicable to solid dose drug product continuous manufacturing processes, although the amount of data to report from advanced control systems will be much greater than that used for traditional analysis.

For section 3.2.P.5.5, Characterization of Impurities, sponsors will need to demonstrate that no new impurities, or higher levels for existing impurities, are formed (e.g., demonstrate that factors such as heat generation or changes in other environmental conditions during the continuous

manufacturing process do not result in stability issues, especially for prolonged manufacturing durations).

Section 3.2.P.8 Stability, is applicable to continuous manufacturing processes. However, the traditional definition for batch sizes that can be put on stability will need to accommodate flexible batch sizes.

6. POST-APPROVAL CHANGES

6.1. Key Elements of Continuous Manufacturing that Support Post Approval Changes

Continuous manufacturing processes are expected to be developed using QbD principles and according to ICH Q8 (R2), Q9 and Q10 guidance documents[6,9,15]. These guidance documents are applicable to continuous manufacturing and ensure a risk-based and science based approach to quality that encourages continuous improvements during the product life cycle.

The development of a product using continuous manufacturing will include a greater emphasis on understanding the interaction between critical variables e.g. raw material attributes and process parameters, and establishing the allowable variability for each parameter which does not impact product quality. It may not be necessary to establish design spaces for all process parameters, however critical sources of variability inherent in the formulation and process should be identified and understood to inform how they will be managed during routine production.

The control strategy developed for a continuous manufacturing process will be based on the integration of empirical data, process models and in-process PAT data. This will ensure that critical variables are identified, monitored and controlled to ensure the production of material of uniform character and quality within specified limits. PAT (including soft sensing) is an integral component of continuous manufacturing, providing timely measurements of critical attributes or surrogates of critical attributes and facilitating scientific understanding of the manufacturing process. The availability of real time continuous monitoring supports continuous improvements and can be leveraged for post approval changes.

6.2. Focus Areas for Post Approval Changes

6.2.1. Changes Post Approval of the Continuous Manufacturing Process

The following are examples of changes that are expected to occur as experience with continuous manufacturing processing is gained over time.

- Increase in the batch size beyond that which was initially verified.
- Change in process parameters within/beyond what was established in the initial design space

- Change in in-process controls or sun-setting of in-process controls (e.g. transitioning to an RTD model for composition vs. use of redundant controls with both an NIR model and an RTD model for composition)
- Change in release testing strategy (e.g. testing on the blend for assay vs. performing assay on final product)
- Change in excipients (grade, vendors), API specifications
- Portability
  - Site changes with identical (or technically compatible) equipment trains
  - Addition of another identical equipment train in the same facility
  - Between non-identical trains – Train equivalence criteria

Depending on the level of process understanding achieved at the time of FDA approval, some of the expected changes listed above, and others similar in nature, may constitute elements of established conditions, while some of them may not be required to define established conditions[28]. Because of the large amounts of information generated by a continuous process during development and manufacturing, companies are likely to gain substantial experience relatively quickly, thus leading to rapid optimization of the sensing and control strategy. Likewise, as the field evolves and more date becomes available regarding sensing and control requirements of different types of products and processes and relative performance capabilities of various versions of similar equipment, some of the expected changes listed above might become routine rather than changes to established conditions.

6.2.2. Changes from an Approved Batch Process to a Continuous Process

The type and extent of change together with the risk profile of the compound will determine how much data from the batch process can be leveraged and what additional studies are required to support this change in the manufacturing process from batch to continuous. If there are no or minimal changes to product composition, the manufacturing process and the specifications from those filed for the batch process, it is expected that information such as stability data from the batch process can be leveraged to support the shelf life of the product manufactured by continuous manufacturing. A biowaiver might be appropriate when formulation changes are small and when in-vitro performance clearly and convincingly demonstrates that product performance is likely to be unaffected. A detailed process and quality comparison between the two manufacturing methods will delineate the differences and guide the development of a risk assessment and the required data to support the transition from a batch to a continuous manufacturing process. Product release and process control requirements are expected to be significantly different for continuous manufacturing especially if the approved product is released using traditional testing and has minimal in process controls.

6.2.3. Changes During Development - Batch Process to Continuous Process

The decision to transition from a batch process to a continuous process during development may occur before or after pivotal clinical data has been generated. If pivotal clinical data has not been generated and formal stability studies have not been initiated the bridging between the batch and continuous process may be conducted via in vitro similarity or a bioequivalence study. However if pivotal clinical data is available using product manufactured by the batch process, the bridging

to the continuous manufacturing process will require extensive in vitro characterization and in some cases, may warrant an in vivo study.

6.3. Risk Evaluation

Continuous drug product manufacturing processes may be developed using the principles outlined in ICH Q8 (R2), Q9 and Q10 guidance documents. This approach will ensure that risks are appropriately identified, characterized and mitigated. Risk assessments, based on prior knowledge and an in-depth understanding of the relationship between the input material properties, the equipment, the process and environmental factors will inform the impact of the changes to product quality and patient safety & efficacy. The availability of a wealth of data from continuous monitoring of the manufacturing parameters as well as the continuous verification plan will be valuable source to assessing the risk of the change to product quality. Additional studies may be performed to further understand the identified risks or mitigate the risks. During implementation of the change, additional testing may be proposed to provide assurance that the change to the approved process is well understood and controlled.

6.4. Filing Requirements

The existing change notification categories (PAS, CBE-30, CBE-0, AR) are available filing options for post approval changes for drug product continuous manufacturing. The risk categorization will inform the change notification category and information from the risk assessment can be used to justify the selected filing option.

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