Regulatory and Quality Considerations for Continuous Manufacturing

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ABSTRACT

This paper assesses the current regulatory environment, relevant regulations and guidelines and their impact on continuous manufacturing. It summarizes current regulatory experience and learnings from both review and inspection perspectives. It outlines key regulatory aspects, including continuous manufacturing process description and control strategy in regulatory files, process validation, and other key GMP requirements. In addition, the paper identifies regulatory gaps and challenges and proposes a way forward to facilitate implementation.

1. INTRODUCTION

In a continuous manufacturing process, input raw materials or mixtures are fed into a process train continuously while the processed output materials are removed continuously. Although the amount of material being processed at any given instance may be relatively small in a continuous manufacturing process, the process may be run over a period of time to generate quantities of finished product with desired product quality. In an end-to-end continuous pharmaceutical manufacturing process, different process steps are sequenced together to form a continuous production line where product removal can occur concurrently at the same rate as the input of raw materials. There may also be situations where a pharmaceutical manufacturing process consists of a combination of batch and continuous process steps.

Continuous manufacturing provides opportunities for improvements in pharmaceutical manufacturing, including:

i. An integrated process with fewer steps (e.g. safer, faster response times, more efficient, shorter times);

ii. Smaller equipment footprint (e.g. potentially small API requirements, more flexibility, lower costs, environmental friendly);

iii. An enhanced development approach (Quality by Design)

iv. Real time product quality information

v. Easier change in scale to accommodate supply needs.

1.1. Current Regulatory Environment

The current regulatory environment supports advancing Regulatory Science and Innovation which may include abandoning some traditional manufacturing practices in favour of *cleaner, more flexible, and more efficient* continuous manufacturing. Regulatory authorities in the three ICH regions and beyond are encouraging industry to adopt new technology as supported by ICH Q8(R2), Q9, Q10 and Q11 and the introduction of Quality by Design (QbD) concepts, emphasizing science and risk based approaches to assure product quality.

The regulatory expectations for assurance of reliable and predictive processing, which is technically sound, risk-based, and relevant to product quality in a commercial setting, are the same for batch and continuous processing.

1.2. Existing Relevant Regulations, Guidelines, and Standards Supporting Continuous Manufacturing

1.2.1. ICH Guidelines

The emergence of ICH Q8 (R2), Q9, Q10, and Q11 guidelines and accompanying ICH Q-IWG Points to Consider (PTC) and Q&A documents emphasized that a prospective science and risk based approach to development and lifecycle management could increase the assurance of quality of pharmaceutical products. Collectively, these guidelines reinforced the adoption of risk–based (Q9), systematic and science–based approaches (Q8 (R2) and Q11), and a robust pharmaceutical quality system (Q10), to establish an increased level of process understanding and product knowledge. While many of the tools described in these ICH guidelines were not, by themselves, new, the implementation of the concepts within a more systematic and integrated framework based on sound science and quality risk management introduced a fundamental paradigm shift in product development and manufacturing.

1.2.2. US FDA Guidances

The *FDA Guidance for Industry PAT-A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance* specifically identifies that the introduction of continuous processing may be one of the outcomes from the adoption of a scientific risk-based approach to process design. Process understanding, control strategies, plus on-line, in-line, or at-line measurement of critical quality attributes (CQA) provide for control strategies that include real time quality evaluation that is at least equivalent to, or better than, laboratory-based testing on collected samples.

1.2.3. FDA Guidance on Process Validation/Continual Verification

FDA Guidance on Process Validation/Continual Verification aligns process validation activities with a product lifecycle concept. The guidance encourages the use of modern pharmaceutical development concepts, quality risk management, and quality systems at all stages of the manufacturing process lifecycle. The lifecycle concept links product and

process development, qualification of the commercial manufacturing process[1], and maintenance of the process in a state of control during routine commercial production. This guidance supports process improvement and innovation, including continuous manufacturing.

1.2.4. ASTM Standards

ASTM E2537 Validation: Standard Guide for the Application of Continuous Quality Verification to Pharmaceutical and Biopharmaceutical describes Continuous Quality Verification (CQV) as an approach to process validation where a manufacturing process (or supporting utility system) performance is continuously monitored, evaluated and adjusted as necessary. It is a science-based approach to verify that a process is capable and will consistently produce product meeting its pre-determined CQAs. With real time quality assurance (that CQV will provide), the desired quality attributes are ensured through continuous assessment during manufacture. Data from production batches can serve to validate the process and reflect the total system design concept, essentially supporting validation with each manufacturing batch.

1.2.5. EU Guidelines

The ICH Guidelines, referenced above, apply in the European Union. EU Guidelines that might be particularly relevant to continuous manufacturing include the *Guidelines for Process Validation* where the concept of continuous process verification is introduced; the *Guideline on NIR* as it is often used as a Process Analytical Technology (PAT) tool for process monitoring and/or control, and the *Guideline on Real Time Release Testing.* Although not required, continuous manufacturing is commonly coupled with Real Time Release Testing (RTRT). Additionally, the European Medicines Agency (EMA) set up a Process Analytical Technology Team in 2003 to support PAT and QbD activities in the EU. The teams act as a forum for dialogue between the Quality Working Party, the Biologics Working Party, and the Good Manufacturing Practice/Good Distribution Practice Inspectors' Working Group.

In summary, global and regional regulations, guidelines, and standards are supportive of innovative pharmaceutical development and manufacturing approaches. Current guidelines may need to be re-evaluated with consideration of continuous manufacturing operations as experience is gained.

2. REGULATORY CONSIDERATIONS

As the pharmaceutical industry and regulatory Agencies gain more experience with continuous manufacturing, several regulatory aspects will need to be explored in order to link the principles and practice. While the current regulatory framework is adequate to allow for continuous manufacturing, traditional concepts may need to be further explored

[1] The term *commercial manufacturing process* refers to the manufacturing process resulting in *commercial product* (i.e., drug that is marketed, distributed, and sold or intended to be sold). In this usage, the term *commercial manufacturing process* does not include clinical trial or treatment IND material.

or challenged to advance the implementation of continuous processes from traditional approaches.

The following aspects are applicable to both batch and continuous processing. In evaluating the differences and similarities between batch and continuous processing, it is important to note that different approaches may be needed for continuous processing:

- The definition of a batch must be stated prior to manufacture. Although each continuous process has unique considerations, one may consider a batch definition based on quantity manufactured or duration of the process.
- In-process controls (IPCs) and sampling considerations will be different. For example, continuous unit operations may have different operating principles; therefore the sampling considerations may differ. Setting up acceptance criteria considering representative tested sample size (i.e. large N) needs to be considered.
- Acceptable procedures for handling deviations including detection and removal of non-conforming material in continuous manufacturing processes must be defined.
- The rationale for testing of a continuous batch must be reconciled against the traditional paradigm. Considerations may be based on time or amount of material impacted by deviation or reaction time for material rejection.
- The importance of the raw material specifications and the lot-to-lot variability of raw materials to the process performance must be considered.
- Sources of variability should be considered during development and controlled during validation and continuous verification.
- The evaluation of manufacturing changes and their impact on product quality needs to reflect relevant risks associated with continuous manufacturing which may be different from batch processes.

Early and frequent communication between manufacturers and regulators is encouraged to ensure alignment and clarify continuous manufacturing requirements. Some regulatory agencies have the opportunity for site visits prior to submission of a regulatory application.[2]

2.1. Development Considerations for Continuous Manufacturing

2.1.1. Process Development

Pharmaceutical companies can use a variety of manufacturing strategies in developing continuous processes for drug substance and drug product manufacture. Possible options would include:

i. A fully continuous process where all drug substance and/or drug product unit operations are sequenced together to form a single production line

[2] US FDA ORA Field Management Directive No. 135

http://www.fda.gov/ICECI/Inspections/FieldManagementDirectives/ucm096042.htm

ii. A fully continuous process as above, but with two or more production lines in parallel

iii. A "hybrid" of batch and continuous mode unit operations.

A continuous manufacturing process emphasizing key design and control aspects would be described in sufficient detail in regulatory submissions similar to traditional/batch manufacturing processes.

The regulatory submission could include a general description of the overall manufacturing strategy. This general description could consist of a brief outline of each unit operation and its mode of operation (i.e. batch or continuous), the material flow, proposed flow rate and total process operation time, critical process parameters, and their ranges and IPC points.

The pharmaceutical development section of the regulatory submission can also include information specific to development and modelling of the continuous process. These aspects may include residence time distributions, system dynamics, disturbance propagation, information on model set up, maintenance, and model improvement.

The definition of a batch or lot has significant regulatory implications, particularly with respect to cGMPs, product recalls, and other regulatory or enforcement actions. Although the definition of a batch or lot could differ for individual continuous manufacturing operations, the underlying regulatory expectation is that the batch or lot is of "uniform character and quality within specified limits." The manufacturing process description would include a clear definition of a batch or lot.

Additional considerations for inclusion in the continuous manufacturing process description are:

- Flow rate of material through the process.
- Factors affecting "scale" of the continuous manufacturing process. For example, "scale out" plans (i.e., multiple lines operated in parallel considered to be the same lot), flow rate ranges, and operation time ranges.
- IPC points.
- Control systems integral to the control strategy. For example, feed-back or feed-forward controls utilized for maintaining a state of control in the system or automated valves used for rejecting material deemed to be out of specification material.

2.1.2. Control Strategy

The same regulatory requirements apply for continuous manufacturing as for batch manufacturing, specifically in that a control strategy should be developed that ensures that the manufacturing process produces product of the intended quality in a reproducible way. Similar to any other mode of manufacturing, control strategy is unique for different products and manufacturing processes. A control strategy developed for a batch process may not be appropriate when the same unit operation is operated in continuous mode.

Therefore, the control strategy should be re-examined if a unit operation that was operated in a batch mode, is now replaced by a unit operation in a continuous mode.

Aspects unique to a continuous operation should be assessed in developing the overall control strategy of a continuous process. As material flows through the system and product is formed continuously over a long period of time, the process, product, or environmental conditions could potentially vary over time resulting in product of variable quality. A robust control strategy is essential to ensure the consistent quality of product formed over the total operation time.

2.1.2.1. Special Considerations for Control Strategy in Continuous Manufacturing

Some aspects to consider in establishing the control strategy for a continuous process are listed below:

- **State of Control**

  A continuous manufacturing process maintaining a state of control provides assurance that the desired product quality is consistently met. There may be situations such as sudden or uncontrolled changes in a process variable, at start-up and shutdown, where assurance is needed that the product is homogeneous and of acceptable quality. However, the process is expected to reach and maintain a state of control after some time. Start-up, shutdown, and transient states need to be considered. The control strategy can establish criteria for determining that the process is under a state of control and procedures for handling process start-up, shutdown, or process variables change. Appropriate process attributes or ranges can be selected for monitoring or a multivariate process control approach can be used. The ability to detect process upsets and institute corrective actions to bring the process back into conformance, such as feedback control, help ensure the consistency of a continuous manufacturing process over the production time.

- **Raw Materials and Intermediates**

  Continuous processing may require additional raw material control, if multiple lots of a raw material are used in a single CM batch. Control approaches should be based on product and process understanding and may include use of PAT tools. The determination of the characteristics of an intermediate product that may or may not be isolated may be more difficult in a continuous process due to the limited sampling ports and high sampling frequencies. The quality of raw materials and excipients must be linked to the product CQAs and the needs of the process.

- **Equipment**

  It is important to consider equipment control aspects for continuous processes. Equipment such as chemical reactors, weight-loss feeders, twin screw blenders, extruders, and tablet presses will need to run for long periods of time and may require special maintenance, calibration, and periodic review to ensure their performance.

- **Uniform Quality and Character of Product**

  The criteria for determining that the product manufactured is of uniform quality and character, the robustness of the process to produce product of desired quality in the presence of variability, and the ability of the system to detect non-conforming product should be established.

- **Product Collection or Rejection**

  Although the continuous process is expected to maintain a state of control, there may be temporary process upsets or disturbances over the total operation time. There may be situations where product made during the disturbance is removed while the remainder of the product is retained. Other situations may warrant rejection of the entire batch instead of a portion of a batch. Establishing a priori criteria for product collection, product rejection, rejection of an entire batch, and indicating how or who makes those decisions prevent ad hoc decisions by manufacturing personnel and helps to ensure the desired quality and consistency of the collected product. The disposition strategy of product obtained during start up and shut down, should also be established.

- **Traceability**

  Traceability of incoming materials to the final product should be understood and documented. Traceability can be supported by data such as residence time distributions and system dynamics. Planned disturbances such as feeder refills and how those disturbances propagate through the system should also be considered.

- **Process Monitoring and Sampling**

  The purpose of the monitoring system is to detect response to planned changes and unplanned disturbances. Potential failure modes of the sampling device should be understood. The samples should be representative of the "whole" and the frequency of measurement or sample acquisition time should consider material flow rate, system dynamics, and unit dose. Flow rate, frequency of sampling, time constants, and residence time distributions: all of these have impact on how we test for quality at any point (raw material attributes, IPCs, final quality) and also how we achieve feedback and feed forward control.

  Consideration can be given to define a flexible test frequency where more testing is expected in periods where there is a greater risk of variability (e.g. following addition of a new lot of input material, or following process parameter adjustments based on feed-forward/ feed-back loops).

- **Risk Assessment and Failure Modes**

  Process robustness is an important factor for consistent operation of a continuous process, which in turn helps to ensure the product formed is of uniform quality and character. A thorough understanding of the risks and failure modes of the process and its associated measurement and control systems allows the development of effective risk mitigation strategies and helps support manufacturing changes and process improvements that may occur over the lifecycle of a product. Knowledge of risks and failure modes is also useful to make risk-based decisions.

- **Scale-Up**

  Scale-up can be achieved in several ways including running longer time, increasing throughput, or parallel units (scale out). Increasing throughput at fixed size units has an effect on residence time distributions and time constants. This effect should be considered during development. Representative sampling may be affected. Physical and physicochemical conditions may be affected by throughput, and criticality of parameters may change following change in throughput.

- **Specifications**

  Specifications will be required as part of the control strategy. Continuous processes may include an RTRT approach for some quality attributes, but it is possible to foresee traditional end product testing on off-line samples. RTRT approaches may require an enhanced sampling plan compared to traditional release testing which may involve a large N that need to be considered when developing the acceptance criteria.

2.1.3. Stability Considerations for Continuous Manufacturing

Regulatory requirements for having adequate stability data does not change between batch manufacturing and continuous processing. There are some differences that should be considered when developing the stability plan.

2.1.3.1. Representative Stability Batches

Since scale may not be a significant risk to stability when using continuous manufacturing, deciding how to determine a representative batch may be different than when using a batch process. A risk assessment should be completed to understand the potential risks of the proposed lot sizes. This risk assessment can then be used to determine a representative lot. The representative lot should have similar characteristics to the lots being manufactured.

2.1.3.2. Considerations for Stability

Stability data should fulfil the initial filing requirements where data is generated on the critical to quality and stability-indicating attributes on representative batches. Representative batches for Annual Stability requirements will also need to be defined.

2.1.3.3. Stability Considerations at Scale-Up

The risks arising from batch scale-up are different for continuous manufacturing. These potential risks may include heat build-up over time, material build-up in the equipment, and others that may be product specific. These risks are usually easily manageable for continuous manufacturing so change in scale may not need additional stability testing.

A change in scale for a continuous process may include volume, time, and/or multiple manufacturing trains that run in parallel. Each of these has its own potential risks to stability that need to be considered. The risk of the scale change to stability should be considered when determining the type of stability testing needed to assess the impact, if any, of scale-up on product stability.

2.1.3.4. Stability Considerations for Site Change / Technology Transfer

When transferring a continuous process from one site to another, the risks to stability should be evaluated. Considerations can include equipment changes, scale changes, and potential location impacts such as different raw material suppliers, and/or different environmental conditions.

2.2. Location of Information in Regulatory Submissions

The development of a continuous manufacturing process is likely to include information obtained from enhanced process development approaches. ICH Q11 and ICH Q8(R2) recommend that process development information be submitted in section 3.2.S.2.6 of the CTD for drug substance and 3.2.P.2 (Pharmaceutical Development) of the CTD for drug product. The two guidance documents also contain specific suggestions for the provision of information from development studies.

In general, the recommendations of ICH Q11 and ICH Q8(R2) could be adopted for placement of information supporting a continuous manufacturing application. ICH Q11 and Q8 recommend the control strategy information be summarized in the specification sections, 3.2.S.4.5 and 3.2.P.5.6, for the drug substance and drug product, respectively. The ICH Q8 and ICH Q11 suggestions for placement of information in a regulatory filing could also be used for continuous manufacturing applications. As in other regulatory submissions, the applicant could clearly indicate where the different information is located in the application. Similar to batch processes, certain aspects of the control strategy are handled under the applicant's pharmaceutical quality system (see ICH Q10). As with other QbD approaches, the current CTD does not provide an optimum platform to present the regulatory development story and considerations should be given to address such gap.

3. QUALITY/GMP CONSIDERATIONS

The flexibility of cGMPs supports new manufacturing technology, such as continuous manufacturing. Points to consider when implementing continuous manufacturing in a cGMP environment are noted below.

3.1. Pharmaceutical Quality Systems

To implement continuous manufacturing in an existing PQS, a site should evaluate its PQS and associated elements to determine if design and content of the PQS should be modified. In addition to the areas described in Q10, e.g., pharmaceutical development, manufacturing, quality, regulatory affairs, and medical) the manufacturing site should establish continuous manufacturing expertise in the quality organization. The change management system for continuous manufacturing processes should include an assessment of risks similar to other traditional batch processes.

3.2. Batch Release

Current regulatory cGMP guidance considers a 'batch' as a defined quantity of product processed in one process or series of processes so that it is expected to be uniform

character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture. This principle applies equally to continuous processes where the amount of material subject to a quality disposition decision could be defined as:

- Process time when all of the material discharged from the process between two specific time points
- Product quantity when a specific quantity of material produced
- Process event when all of the material produced between two specific process events
- Raw material quantity input when all of the material that is "intended" to contain a specific lot or quantity of a specified input material.

If continued state of control operation is demonstrated, it becomes possible to designate large quantities of material as 'homogenous' even though different lots of raw materials and different processing conditions may have been used. The key is to have clearly defined criteria, which describe state of control operation, and to establish the product and process data, which demonstrate continued conformance with these criteria.

Continuous manufacturing within a controlled and reproducible operation may have periods of process perturbation. Therefore during development, these perturbations should be considered and criteria developed to define the state of control. Procedures are needed for material traceability. This allows for a defined period of diversion of waste should adverse perturbations occur.

Material traceability and designation of either large or small quantities of material which are deemed to be homogeneous is vital in the event of problems with product quality such as contamination, raw material, recalls, or other GMP failures. An understanding of material flow in the system is essential to divert or recall the potentially affected material. Close monitoring of product and process data may allow further decisions to be made, such as bringing the process back to target via process control measures, which could help to minimise the impact of any process failures.

3.3. Start-Up and Shutdown Procedures

During periods of start-up, shutdown, and processing of material, it is possible that not all unit operations within a continuous production line will be in a state of control at the same time. For example:

- During shutdown, material may not be fed and discharged simultaneously. Material will continue to be processed and discharged after the feeding operation has stopped.
- Where small amounts of material are produced, the first unit operation could already be shut-down while the material is processed further.

The start from which onward material gets collected for later release has to be defined. The time point when the process is in a state of control, and significant process

parameters, in-process material attributes, CPPs, and CQAs are all within their specified criteria, needs to be defined. The same determination is necessary for shut-down periods and for transient adverse perturbations requiring material diversion.

Within process verification, the ability of the process to reach and detect the period of normal production should be demonstrated.

The time available for a given process transformation is determined by the residence time of the material in a specific process environment and needs to accommodate the necessary reaction time for completion. As the material flows through the system, rate-limiting elements within the process must be considered to ensure that the required end point condition can be met within the time available (e.g., required process to complete a chemical reaction or drying operation). There can be potential impact on product quality of various time constants of the process and the equipment, which should be considered, such as the effects of thermal mass, especially during start-up and transient conditions.

An understanding and subsequent verification of the various time constants of the process is specifically important in determining the expected behavior of the process during start-up and shutdown and hence the impact on quality decisions regarding the disposition of material manufactured during this period.

3.4. State of Control: Product Collection and In-Process Sampling

A state of control provides assurance of continued process performance and product quality as described in ICH Q10.

Acceptance criteria based on appropriate monitoring at an adequate frequency must be established to ensure that the entirety of the material subjected to the release decision is compliant to the applicable specifications. Diversion and/or rejection of material, which does not meet acceptance criteria, must be justified by proper demonstration that the diversion/rejection decisions are based on reliable data and proper understanding of process dynamics.

Consideration should be given to confirm the ability of the system to produce consistent product over extended operation and to understand potential mechanisms of failure and degradation of performance together with suitable methods of detection. Risk analysis techniques including practical tests and/or modeling tools should be employed to ensure that any impact on product quality is understood and appropriately managed overall operating states, and especially during normal operations.

In order to define the period of product collection, the process residence time and residence time distribution must be understood and quantified during start up and normal operation conditions as well as during shutdown conditions until product is no longer collected. In particular, an understanding and quantification of the residence time distribution may be used to determine which material may have been affected by a deviation in process conditions and hence the range of product within the scope of any investigation or disposition decision.

The maximum length of time over which the process is run may be determined by monitoring specific product attributes or process parameters and equipment capability rather than by validating a single fixed length of run time.

Appropriate sampling, testing, quality control procedures, and equipment mechanisms to detect and reject materials, which are out of specification, are necessary. In order to ensure that a process parameter or product attribute cannot move outside the predefined acceptable process window or acceptable range without being detected, it is important to ensure that the control and monitoring system is able to take measurements at a frequency which is appropriate to the dynamic response time of the parameter or attribute. Measurement frequency should consider the intrinsic process risk (e. g. higher risk at lower API dose), the known process variability, and the required residence time in the equipment to complete transformation (e. g. higher risk at faster throughput).

3.5. Process Validation and Continuous Process Verification

Within process validation and continuous process verification, process robustness and reproducibility should be evaluated. The development of a continuous process should follow established principles, which are applied generally within pharmaceutical process development. Existing guidances and standards should also be consulted for process verification/validation and Continuous and/or Continued Process Verification (CPV). The requirements for including process validation and lifecycle management information in the regulatory submission can be expected to be the same as that for batch processes.

In verifying the ability of the system to control and achieve the specified performance, the following should be verified for continuous processes:

i. The process conditions, which determine that the system is under normal state of control including verification that CPPs and CQAs, should be within target range.

ii. The ability of the process control system to reach and detect the start of acceptable product production. In order to demonstrate this ability as part of the process verification, a set of start-up and shutdown activities may be included. The number of start-ups and shutdowns included in the verification activities may be determined based on a risk analysis for a given process and the unique critical considerations for that process including process robustness, and number and inter-relationship of CPPs/CQAs.

iii. The ability of the system to reach and maintain the intended process conditions over the entire process needs to be evaluated. The expected process run time and worst case (longest) process run time should be considered as a component of the process validation activities.

iv. The ability to detect excursions from the target CPP or CQA values requiring the diversion of non-conforming material based on sufficient understanding of process dynamics or shutdown of the process.

v. The impact of changes in the process production rate and/or equipment scale changes on the process dynamics should also be considered.

vi. The goal of the final validation stage is continual assurance that the process remains in a state of control (the validated state) during commercial manufacture.

vii. The validation data should be statistically trended and reviewed by trained personnel. The information collected should verify that the quality attributes are being appropriately controlled throughout the process.

    a. Quantitative, statistical methods are recommended whenever appropriate and feasible.

    b. Scrutiny of intra-batch as well as inter-batch variation should be considered.

CPV as an alternative validation approach may be particularly well suited to the evaluation of continuous manufacturing processes. It can utilize in-line, on-line, or at-line monitoring or controls to evaluate process performance. These are based on product and process knowledge and understanding. Monitoring can also be combined with dynamic control systems in order to adjust the process to maintain output quality. This capability also provides the advantage of enhanced assurance of intra-batch uniformity, fundamental to the objectives of process validation. Some process measurements and controls in support of RTRT can also play a role in CPV.

Using this approach, data from production batches can serve to validate the process and demonstrate processing in accordance with the total system design concept, essentially supporting validation with each manufacturing batch replacing a conventional process validation approach (e.g. 3-batch validation at set-point) that was historically used.

As with traditional batch manufacturing, system qualification of equipment and other supporting systems, including PAT and/or automation, is necessary. This may be especially critical if some systems are providing real-time monitoring and control of a continuous manufacturing process.

3.6. Material Traceability in a Continuous Manufacturing Train

For any specific quantity of product produced from a continuous processing system and released to the market, it must be possible to reliably link the relevant process information to the specific quantity of product in a timely manner and to identify the lots of raw materials from which it has been manufactured. This includes an understanding of residence time and residence time distribution at relevant flow rates and operating conditions. An appropriately reliable and timely link between relevant product quality information and any specifically identified product has to be demonstrated for the purpose of later release, such as diversion of unacceptable product during the process.

The overall flow of product in the system or subsections of the system has to be understood, including the ability to account for material which may be removed deliberately from the system for sampling, unintentionally lost from the system due unforeseen events, or diverting.

3.7. Handling of Raw Material and In-Process Material

Continuous processing may pose challenges due to behaviours of both equipment and material, for example starting materials in a hopper, or intermediates in process which

occur gradually over a long period and which are not easily observed during batch processing or short tests runs. The handling and flow properties of materials to be processed should be determined as early as possible within the development of the product such that the process equipment may be designed appropriately. Transport processes may cause some degree of transformation (e.g. segregation attrition of powders) and therefore careful consideration should be given.

Suitable risk analysis, practical tests, and modelling techniques should be considered in order to determine and evaluate potential challenges in maintaining stable process conditions during the operation of a continuous process over the full length of the required production run. Consideration should be given to the potential for undesirable build-up of material due to physical and chemical processes, stability of starting materials, or intermediates being held in buffer tanks.

3.8. Detection and Treatment for Non-Conformity

A key component in any quality system is handling non-conformities and/or deviations. While process and product understanding are extremely important, unexpected discrepancies will undoubtedly occur during the product lifecycle. These issues may cause the quality system to question the existing process and product understanding and may require additional process development. A robust Corrective And Preventive Action (CAPA) system is integral to product and process improvement. The methodology used should result in product and process improvements and enhanced product and process understanding.

There are some key elements for consideration in a continuous manufacturing process. The process control/monitoring system shall be adequately developed to recognize a normal process, and be able to identify when the data are divergent enough to represent a departure that could have direct impact on quality. In these cases, the product needs to be diverted for rejection/waste. As a consequence, it is possible that not all of the materials that were originally fed into the process, as part of the original single manufacturing order, will be in the finished product intended for release to the market.

Continuous manufacturing may also have more complex in-process controls and monitoring with the potential for unintended failure modes, which have to be considered in setting a robust control system.

Handling of non-conformities for continuous manufacturing and batch manufacturing are generally similar. Some key differences for consideration are described below:

3.8.1. Personnel Procedures and Training

In a robust pharmaceutical quality system, when new technology such as continuous manufacturing and PAT tools are implemented, it is important to evaluate the impact, if any, on existing quality, production, and engineering procedures. Procedures that define who is responsible for halting and resuming operations, how non-conformities are documented, investigating discrepancies, and taking remedial action may need to be modified based on the new technology. New procedures and/or modifications will require additional personnel training.

3.8.2. Material Carry-Over

It is important to ensure that any investigations are properly extended to other batches of the same drug product. Thus, understanding how the facility defines a batch is critical to ensuring that the investigation is properly extended to related batches. The amount of allowable carryover volume should be considered.

3.8.3. Material Diversion

Establishing thorough procedures to describe handling of non-conformances including out-of-specification or out-of-trend results that requires product stream diversion during manufacturing is critical. Procedures describing when the product stream should be diverted and when collection should be re-initiated needs to be decided prior to the non-conformance occurring. If non-conforming material is detected it should be diverted at the next appropriate point. The impact of forward processing should be evaluated. The in-process monitoring detects that a certain amount of material needs to be diverted. This diversion should be investigated before determining the diverted and good material disposition. In batch manufacturing, this process may be described as partial batch rejection and raises many questions about the robustness of the process and quality of the accepted material.

3.8.4. Production Floor Product Monitoring

PAT tools are more likely to be implemented in continuous manufacturing processes on the production floor (in-line, at-line, or on-line). If a discrepancy is identified on the production floor, it should be investigated prior to material disposition. For example, if in-line testing results are trending towards failure, end product testing cannot solely be used to release associated material without an associated investigation.

If a breakdown in the monitoring equipment occurs, this should also be investigated. A procedure should be established for the use of alternative testing or monitoring approaches in cases of equipment failure. The alternative approach could involve use of end product testing or other options, while maintaining an acceptable level of quality.

3.8.5. Raw Material Variability

For continuous manufacturing processes, it is important to consider raw material variability as a potential root cause when performing an investigation. In a batch process, multiple raw material batches are typically mixed at the start of manufacturing. This may not be true for continuous manufacturing, where different lots of raw material can be used during the production campaign. Multiple raw material lots used in a single product batch, though they might meet specification, could introduce variability into the finished product.

3.9. Cleaning Validation

Cleaning and cleaning validation considerations for continuous manufacturing equipment and systems are primarily the same as those for non-continuous manufacturing equipment and systems. For continuous manufacturing, either dedicated or non-dedicated

equipment may be utilized. Principles for determining acceptance criteria for cleaning agent, bioburden, endotoxin, and degradation products for cleaning validation of dedicated equipment are essentially the same as for non-dedicated equipment.

If dedicated equipment is utilized for continuous manufacturing, cross-contamination of the active ingredient from the previous product to the next product is not an issue. Therefore, cleaning validation related to the active itself is generally not considered a requirement for dedicated equipment. However, cleaning validation should be considered for dedicated equipment if carryover of the cleaning agent or the contribution of bioburden or degradation by-products to the next manufactured batch is a concern. Manufacturers should conduct risk assessments for all cleaning scenarios to determine the need for cleaning validation to comply with product quality including residues and lot integrity and regulatory expectations. It is considered to be best practice to document effectiveness of a cleaning process for dedicated equipment even if "visually clean" is the only criteria.

The cleaning process and frequency of cleaning should be defined and the effectiveness verified periodically.

The design and verification of the cleaning process should consider:

i. Material holdup and buildup. on equipment, piping, instruments (e.g. on-line analyzers, sensors), filters
ii. Degradation of the material within the process
iii. Microbiological growth
iv. Formation of chemical films
v. Cleaning agent removal, if applicable
vi. Product change-over, if applicable
vii. Equipment Size and complexity, e.g. equipment used for continuous manufacturing may be smaller in size and may have more intricate parts and components that maybe more difficult to clean.

The cleaning frequency for continuous manufacturing equipment and systems may be defined in terms of:

i. Elapsed operating time
ii. Quantity of material processed
iii. History of process conditions or deviations
iv. Product change-over, if applicable

Cleaning Strategies employed for Continuous Manufacturing can include:

i. Stopping production or diverting or tagging material as non-releasable material (e.g. if reliant on a single analyser that requires attention)

ii. Providing a second, duplicate piece of equipment or instrument (e.g. analyser)

iii. In process cleaning of instruments such as sensors (e.g. air washes)

3.10. Equipment Failure

Continuous processing may pose challenges due to performance of the equipment, which occur gradually over a long period and hence which are not easily observed during batch processing or short tests runs. Sudden equipment failures can occur which have to be addressed. The control system has to be designed in a way that those effects are detected and addressed.

Suitable risk analysis, practical tests, and modeling techniques should be considered in order to determine and evaluate potential challenges in maintaining stable process conditions during the operation of a continuous process over the full length of the required production run.

Where one unit operation within a process line is determined to be disproportionally vulnerable for example due to degradation or lack of robustness, or prone to equipment failure then an appropriately designed control system has to be designed and strategies to maximize the potential run time may be considered. Such considerations may include rapid change over or redundancy/parallelization/duplication of critical equipment elements.

4. REGULATORY AND QUALITY CONSIDERATION OF BRIDGING EXISTING BATCH MANUFACTURING TO CONTINUOUS MANUFACTURING

There may be situations where a continuous manufacturing process is proposed in the regulatory submission while a different process, such as a batch process, is used to make the clinical, bioequivalence, or registration stability batches. A company may also wish to introduce a continuous process as a post-approval manufacturing change. In such situations, a case-by-case approach can be used to assess the risk of the process change to determine the type of bridging information that would be appropriate to support the change. Changes should be summarized and justified with appropriate *in-vitro* and/or *in-vivo* comparison studies.

A change from batch to continuous is likely to result in changes to equipment, process parameters, control strategy, and facility or manufacturing area. A comparison of the two processes and the input materials (or formulation) is a starting point for assessing the risk of the process change. In addition to differences within individual unit operations and equipment, the overall processes may need to be assessed holistically as differences in system dynamics can contribute to risk.

Factors such as dosage form, strength, drug load, potency, release profile, and route of administration can also be factors that impact risk. For example, the risk of a high drug load immediate-release tablet is likely to be less than that of a low drug load extended release-tablet. A discussion of the proposed change and the bridging strategy with the

respective Regulatory Agency may be advisable to gain agreement prior to conducting the studies.

Some aspects to consider when bridging batch and continuous processes are discussed below.

4.1. Physicochemical Equivalence Considerations

A change from batch to continuous manufacturing would necessitate establishing physicochemical equivalency. To support the change from batch to continuous operation, an evaluation can include a comparison of individual unit operations, process parameters, equipment, CQAs, and the control strategy. To support chemical equivalency, comparative batch data, particularly with respect to physical properties, impurity profiles, and drug release profiles, and bridging stability data can be provided.

4.2. Bioequivalence Considerations

In many instances, the continuous process may be based on the same unit operations and formulation as used for the batch process. The risk of change to product quality attributes (e.g., polymorphicity, dissolution, impurities, stability, etc.,) may be low and demonstration of chemical equivalence may be sufficient to support the change. However, there could be situations, albeit rare, when significant changes or novel approaches are used in moving from batch to a continuous process. For example, the continuous process could incorporate a novel crystallization method that changes crystal form or a significant formulation change. Also, the drug product characteristics (e.g., a dosage form with a complex release profile or a very low drug load) may need to be considered in evaluating risk. Significant changes or high-risk products may need to be bridged by bioequivalence studies.

5. GLOSSARY AND DEFINITIONS

5.1. Batch Definition

An important aspect of Continuous Manufacturing is the definition of a batch. There are specific references to "batch" and "lot" in the US Code of Federal Regulations, which are applicable and need to be considered.

21CFR 210.3

- The definition of a **batch** is 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. Therefore batch refers to the quantity of material and does not specific the mode of manufacture.
- **Lot – 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.

The 21 CFR definitions for both "batch" and "lot" are applicable to continuous manufacturing.

21 CFR 211

Documentation of Manufacturing 21CFR 211.188

- Batch product and control records shall be prepared for each batch of drug product produced and shall include complete information relating to the production and control of each batch

While the regulations in the CFR provide flexibility in the area of documentation, the definition of a batch/lot at collection is not specifically described.

ICH Q7

A Batch or Lot is defined as:

A specific quantity of material produced in a process or series of processes so that it is expected to be homogeneous within specified limits. In the case of *Continuous production*, a batch may correspond to a defined fraction of the production. The batch size can be defined either by a fixed quantity or by the amount produced in a fixed time interval

The batch definition is a fundamental element of continuous processes. It is linked to in-process testing, specifications, batch disposition, and many critical aspects of cGMP compliance.

ICH Q10

State of Control: A condition in which the set of controls consistently provides assurance of continued process performance and product quality (ICH Q10).

6. REFERENCES

ICH Quality documents Q3, Q7, Q8 Q8(R2),Q9,Q10,Q11

FDA Guidance for Industry PAT A Framework for Innovative Pharmaceutical Development, Manufacturing and Quality Assurance

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[1] J. Woodcock, FDA, AAPS Annual Meeting October 2011

http://www.fda.gov/ScienceResearch/AboutScienceResearchatFDA/ucm342928.htm

[1] PhRMA White Paper Implementation and Application of Quality by Design Feb 2013

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/02/WC500162136.pdf

EU Guidelines Guidelines for Process validation

Guideline on NIR

Guideline on Real Time Release testing,

ASTM Standards E2537

21CFR references are in the Glossary section

21CFR210.3

21CFR211.118