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Standard Guide for Application of Continuous Process Verification to Pharmaceutical and Biopharmaceutical Manufacturing[1]

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1. Scope

1.1 This guide describes Continuous Process Verification as an alternate approach to process validation where 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 predetermined critical quality attributes. Continuous Process Verification (ICH Q8) is similarly described as Continuous Quality Verification.

1.2 Pharmaceutical and biopharmaceutical product manufacturing companies are required to provide assurance that the processes used to manufacture regulated products result in products with the specified critical quality attributes of strength identity and purity associated with the product safety and efficacy. Process validation is a way in which companies provide that assurance.

1.3 With the knowledge obtained during the product lifecycle, a framework for continuous quality improvements will be established where the following may be possible: *(1)* risk identified, *(2)* risk mitigated, *(3)* process variability reduced, *(4)* process capability enhanced, *(5)* process design space defined or enhanced, and ultimately *(6)* product quality improved. This can enable a number of benefits that address both compliance and operational goals (for example, real time release, continuous process improvement).

1.4 The principles in this guide may be applied to drug product or active pharmaceutical ingredient/drug substance pharmaceutical and biopharmaceutical batch or continuous manufacturing processes or supporting utility systems (for example, TOC for purified water and water for injection systems, and so forth).

1.5 The principles in this guide may be applied during the development and manufacturing of a new process or product or for the improvement or redesign, or both, of an existing process.

1.6 Continuous process verification may be applied to manufacturing processes that use monitoring systems that provide frequent and objective measurement of process data in real time. These processes may or may not employ in-, on-, or at-line analyzers/controllers that monitor, measure, analyze, and control the process performance. The associated processes may or may not have a design space.

1.7 This guide may be used independently or in conjunction with other proposed E55 standards to be published by ASTM International.

2. Referenced Documents

2.1 *ASTM Standards:*[2]

E2363 Terminology Relating to Process Analytical Technology in the Pharmaceutical Industry

2.2 *Other Publications:*

ICH Q8 (R2) Pharmaceutical Development (Step 4 version), November 2009[3]

ICH Q9 Quality Risk Management (Step 4 version), November 2005[3]

ICH Q10 Pharmaceutical Quality System (Step 4 version), June 2008[3]

ICH Q8, Q9, and Q10 Questions and Answers (R4), November 2010[3]

ICH Q11 Development and Manufacture of Drug Substances (Step 4 version), May 2012[3]

Pharmaceutical CGMPs for the 21st Century —A Risk-Based Approach[4]

[1] This guide is under the jurisdiction of ASTM Committee E55 on Manufacture of Pharmaceutical and Biopharmaceutical Products and is the direct responsibility of Subcommittee E55.03 on General Pharmaceutical Standards.

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[2] For referenced ASTM standards, visit the ASTM website, www.astm.org, or contact ASTM Customer Service at service@astm.org. For *Annual Book of ASTM Standards* volume information, refer to the standard's Document Summary page on the ASTM website.

[3] Available from International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), ICH Secretariat, c/o IFPMA, 15 ch. Louis-Dunant, P.O. Box 195, 1211 Geneva 20, Switzerland, http://www.ich.org.

[4] Available from Food and Drug Administration (FDA), 5600 Fishers Ln., Rockville, MD 20857, http://www.fda.gov.

Guidance for Industry, PAT —A Framework for Innovative Pharmaceutical Development, Manufacturing and Quality Assurance, September 2004[4]

Guidance for Industry, Process Validation —General Principles and Practices, January 2011[4]

Guideline on Process Validation for Finished Products — Information and Data to be Provided in Regulatory Submissions, February 2014[5]

Guidelines for Good Manufacturing Practice, Volume 4 — Medicinal Products for Human and Veterinary Use, Annex 15: Qualification and Validation, March 2015 (effective October 2015)[6]

Pharmaceutical Inspection Co-operation Scheme, Annex 15 —Qualification and Validation, April 2015[7]

Good Manufacturing Practice, Annex 2 —Qualification and Validation, May 2015 (effective December 2015)[8]

3. Terminology

3.1 For definitions of terms used in this guide, refer to Terminology E2363.

4. Significance and Use

4.1 Application of the approach described within this standard guide applies science-based concepts and principles introduced in the FDA's initiative on pharmaceutical CGMPs for the 21st century.[4]

4.2 This guide supports, and is consistent with, elements from ICH Q8 – Q11 and guidelines from USFDA, European Commission, Pharmaceutical Inspection Co-operation Scheme, and the China Food and Drug Administration.[8]

4.3 According to FDA Guidance for Industry, PAT, "With real time quality assurance, 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." In other words, the accumulated product and process understanding used to identify the Critical Quality Attributes (CQAs), together with the control strategy, will enable control of the CQAs, providing the confidence needed to show validation with each batch. This is as opposed to a traditional discrete process validation approach.

5. Key Concepts

5.1 This guide applies the following key concepts: *(1)* science-based approach, *(2)* quality by design, *(3)* product and process understanding, *(4)* quality risk management, and *(5)* continuous improvement.

5.2 *Science-based Approach:*

5.2.1 Product and process information, as it relates to product quality and public health, should be used as the basis for making science- and risk-based decisions that ensure that a product consistently attains a predefined quality.

5.2.2 Examples of product and process information to consider include: Critical Quality Attributes (CQAs), Critical Process Parameters (CPPs), control strategy information, and prior production and development experience.

5.3 *Quality by Design:*

5.3.1 Quality by design concepts may be applied in the design and development of a product and associated manufacturing processes to ensure critical quality attributes can be accurately and reliably predicted (for example, for materials used, process parameters, manufacturing, environmental and other conditions).

5.3.2 Quality by design, when built into an organization's quality system, provides a framework for the transfer of product and process knowledge from drug development to the commercial manufacturing processes for launch, post-development changes, and continuous improvement. It is this knowledge which enables the organizational understanding that is required for effective risk management and decision excellence. Successful continuous process verification can only be achieved if systems exist to capture and codify this knowledge into actionable elements for process monitoring and control as part of the quality systems and production framework.

5.3.3 Continuous process verification can be an alternate to traditional process validation.

5.4 *Product and Process Understanding:*

5.4.1 Product and Process understanding accumulates during the development phase and continues throughout the commercialization phase of the product lifecycle. In the desired state, "A process will be considered well understood when *(1)* critical sources of variability are identified and explained; *(2)* variability is managed by the process; and *(3)* product quality attributes can be accurately and reliably predicted over the design space established for materials, process parameters, manufacturing, environmental, and other conditions." (FDA Guidance for Industry, PAT)

5.4.2 Product and process understanding can reduce the burden for validating systems by focusing on aspects that are critical to product quality. Systems are verified that are intended to monitor and control biological, physical, or chemical attributes, or combinations thereof, of materials and processes.

5.5 *Quality Risk Management:*

5.5.1 Quality risk management approaches should be used as a proactive means to identify potential quality issues during product development and manufacturing to further ensure the high quality of the drug product to the patient.

5.5.2 Quality risk management can, for example, help guide the setting of specifications and process parameters for drug manufacturing, assess and mitigate the risk of changing a process or specification.

5.5.3 Risk management should be an ongoing part of the quality management process and the output/results of the risk

[5] Available from European Medicines Agency (EMA), 30 Churchill Place, Canary Warf, London E14 5EU United Kingdom, http://www.ema.europa.eu/ema.

[6] Available from European Commission (EC), 1049 Brussels, Belgium, http://ec.europa.eu.

[7] Available from Pharmaceutical Inspection Co-operation Scheme (PIC/S), 14 Rue du Roveray, 1207 Geneva, Switzerland, http://www.picscheme.org.

[8] Available from China Food and Drug Administration, Building #2, 26 Xuanwumen West Street, Xicheng District, Beijing, 100053, P.R. China, http://eng.sfda.gov.cn.

management process should be reviewed to take into account new knowledge and experience.

5.6 *Continuous Improvement:*

5.6.1 Improved process understanding provides opportunities for further risk mitigation by optimizing process design and control.

5.6.2 Comprehensive statistical process data analysis, where applicable, should be used to provide the rationale for justifying changes to measurement, control, and testing requirements along with associated specifications for each product.

6. Continuous Process Verification

6.1 *Overview:*

6.1.1 Continuous learning and quality verification occurs over the lifecycle of a product and should include the following aspects:

6.1.1.1 Product understanding and process understanding,

6.1.1.2 Continuous process and quality monitoring and control,

6.1.1.3 Process performance evaluation,

6.1.1.4 Acceptance and release, and

6.1.1.5 Continuous process improvement.

6.1.2 Manufacturers should have a comprehensive and current quality system in place. Robust process development and quality systems will promote process consistency by integrating effective knowledge-building mechanisms into routine operations.

6.1.3 Science-based approaches should be applied at each stage of the process.

6.1.4 Quality risk management should be applied at each stage of the process.

6.1.5 A continuous process verification approach may be combined with a traditional validation approach for certain steps of the manufacturing process. The entire manufacturing process is thus a hybrid[6,7,8] of the two approaches.

6.2 *Product and Process Understanding:*

6.2.1 In a current quality systems manufacturing environment for new products, the significant characteristics of the product being manufactured should be defined from design through the full lifecycle to retirement, and appropriate levels of control should be exercised over changes.

6.2.2 Process characterization studies performed during process development establish initial process knowledge.

6.2.3 Further process characterization studies performed during scale-up establish further understanding of the process and control requirements. Risk assessments to define and justify the final CPPs and CQAs may be an iterative process as the understanding of the process increases.

6.2.4 This information is documented in summary documents (for example, product and process development report, formulation development summary, or process knowledge report). Here Critical Process Parameters (CPP) are identified in order to meet the Critical Quality Attributes (CQA). These are defined, justified, and documented.

6.2.5 For existing processes, commercial experience and historical data provide further process knowledge and understanding.

6.2.6 The use of conventional data collection plans, process control charts, production record data, and current process analytical technology systems during manufacture will allow for the collection and further analysis of real- or near-time data.

6.2.7 The use of multivariate data analysis approaches in conjunction with knowledge management systems can allow the identification of product variation and process control variables that are critical to product quality and process performance.

6.2.8 Risks to product quality may be identified, assessed and mitigated by the identification and establishment of critical process parameters whereby the critical quality attributes are assured. Results from risk assessments will provide input to the process control strategy. Knowledge gained from similar processes and equipment performance may be leveraged in process risk management.

6.3 *Continuous Process and Quality Monitoring and Control:*

6.3.1 A quality system approach calls for the manufacturer to develop procedures (based on product and process understanding) that monitor, measure, analyze, and control the process performance (including analytical methods or statistical techniques, or both).

6.3.2 A process control strategy should be developed and documented. The strategy will describe the elements necessary to assure the process is valid and suitable for commercialization; the plan for monitoring, measuring, analyzing, and adjusting (if necessary) the critical aspects of manufacturing steps/unit operations; and how this plan will ensure process performance and product quality. The measurement frequency should be sufficient to identify process excursions related to critical quality attributes.

6.3.3 The process control strategy may document or reference the following:

6.3.3.1 The steps/unit operations included in the scope of the control strategy document.

6.3.3.2 The critical quality attributes, critical quality parameters, intended operating ranges that need to be monitored and controlled, and acceptance criteria as determined through the quality by design approach.

6.3.3.3 The facility environment and equipment operating parameters.

6.3.3.4 The associated methods, accuracy, and frequency of monitoring and control to facilitate timely feedback/feed forward and appropriate corrective action and preventive action.

6.3.3.5 Process measurement and data collection techniques may allow for the collection and further analysis of real- or near-time data, for example, of in-process or final product CQAs (or both), process end-points, and CPPs.

6.3.3.6 Consideration should include raw materials and component variability, in-process testing, end product testing, and evaluation required to demonstrate the performance of the process.

6.4 *Process Performance Evaluation:*

6.4.1 Continuous process verification requires documentation or records including a decision as to the validated state. Collectively these documents will provide the necessary evidence to show that the process operates in a validated state, and

the ongoing monitoring, control, and analysis provides assurance that the process continues to operate in a state of control. A decision as to the fitness for use should be in place prior to commercialization.

6.4.2 An ongoing process monitoring program will provide an opportunity to conduct an evaluation of process performance to confirm that the process is performing as intended. This is also called Continued Process Verification (FDA).[4]

6.4.3 The process performance evaluation may include the following:

6.4.3.1 A review of the manufacturing data for CPPs and CQAs against the acceptance criteria.

6.4.3.2 An evaluation of the process performance, for example using process capability analysis. If statistical process capability analysis is used, it should include an assessment of process controls and parameters that are critical to product quality.

6.4.3.3 A system for detecting unplanned departures from the process as designed and the impact of deviations on the process validation.

6.4.3.4 Review of variation, considering timely assessment of defect complaints, out-of-specification findings, process deviation reports, process yield variations, batch records, incoming raw material records, and adverse event reports.

6.4.3.5 A conclusion whether the process is considered validated and recommendations for any modifications to the process understanding (for example, CPPs, Design Space) or control strategy based on the increased process understanding acquired during the performance evaluation.

6.4.3.6 A documented recommendation or plan on the appropriate frequency for routine process performance evaluation, the data to be reviewed, and how the data will be analyzed.

6.4.4 Process capability assessment may serve as a basis for determining the need for changes that can result in process improvements and efficiency.

6.4.5 The use of process capability analysis of variables that are critical to product quality and performance may improve process understanding and provide a level of confidence that each batch conforms to established quality attributes to enable the real-time release of product. This may justify minimizing end product testing and places greater emphasis on the results of in-process testing (whether performed in-line, on-line, at-line, or off-line in an analytical laboratory).

6.4.6 The evaluation of process data may be documented in product quality reviews. The information from trend analyses can be used to continually monitor quality, identify potential variances before they become problems, bolster data already collected for the quality review, provide statistically sound data for further process optimization and control, or any combination thereof.

6.5 *Acceptance and Release:*

6.5.1 A review of the adherence to the process control strategy, acceptance criteria and process monitoring requirements, manufacturing documentation, and an evaluation and documentation of the process data should be conducted at a predefined stage of a process or batch to make an assessment and conclusion of the process validity, and hence the suitability for release of the final product. This conclusion, in addition to a GMP assessment for batch release, should be made prior to commercialization.

6.5.2 Product and process understanding, control strategies, and measurement of critical attributes that relate to product quality provides a scientific risk-based approach. This may provide a level of confidence that each batch conforms to established quality attributes to enable the real-time release (RTR) of the final product.

6.5.3 Real-time release may be considered comparable to alternative analytical procedures for final product release. This should minimize end product testing and place greater emphasis on the results of in-process testing (whether performed on-line, at-line, or in an analytical laboratory).

6.5.4 For some products, the different stages of the manufacturing process will be discrete, thus allowing monitoring and sampling at critical parts of distinct stages of the process. For other products, the manufacturing process may be more or less continuous, necessitating a more integrated process monitoring. It is therefore not possible to specify in a guideline, specific details of how real-time release can be applied. However, the general basis upon which real-time release may be applied should include science and documentation that shows:

6.5.4.1 Process understanding.

6.5.4.2 The process remained within the acceptance criteria defined in the control strategy.

6.5.4.3 The level of process control delivered the required product quality attributes.

6.5.4.4 There is a relation between process monitoring and product CQAs.

6.5.4.5 Clear, specified procedures are in place describing the reporting and actions to be taken on approval/rejection.

6.6 *Continuous Process Improvement:*

6.6.1 Routine process performance evaluation should be performed at an appropriate frequency and the data reviewed and analyzed. To support continuous improvement, the results of any product or process evaluation, or both, should be used to further enhance existing process knowledge and understanding and assess the effectiveness of the process design. As experience is gained in commercial production, opportunities for process and system improvements should be sought based on periodic review and evaluation, operational and performance data, and root-cause analysis of failures. This will allow an iterative process of design improvement throughout the product lifecycle.

6.6.2 Continuous analysis of the process may be achieved through a number of methods. The application of statistical tools (for example, process capability) may be used when sufficient data are available.

6.6.3 Change management should provide a dependable mechanism for prompt implementation of manufacturing and process improvements resulting from knowledge gained during a product's lifecycle.

7. Keywords

7.1 continuous improvement; continuous process monitoring; continuous process verification; process capability analysis; process control strategy; process understanding; real-time release