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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.

1.8 *This international standard was developed in accordance with internationally recognized principles on standardization established in the Decision on Principles for the Development of International Standards, Guides and Recommendations issued by the World Trade Organization Technical Barriers to Trade (TBT) Committee.*

2. Referenced Documents

2.1 *ASTM Standards:*[2]

E2363 Terminology Relating to Manufacturing of Pharmaceutical and Biopharmaceutical Products in the Pharmaceutical and Biopharmaceutical 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]

[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 E55.11 on Process Design.

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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.

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]
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.

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

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.