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Standard Guide for Verification of Process Analytical Technology (PAT) Enabled Control Systems[1]

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1. Scope

1.1 This guide describes the verification of process analytical technology (PAT) enabled control systems using a science- and risk-based approach. It establishes principles for determining the scope and extent of verification activities necessary to ensure that the PAT-enabled control system is fit for purpose, properly implemented, and functions as expected.

1.2 In this guide, a PAT-enabled control system is considered to be the system that adjusts the manufacturing process using timely measurements (that is, during processing) of attributes of raw and in-process materials to determine responses that assure the process remains within specified boundaries and minimizes variability in the output material. The overall aim of the PAT-enabled control system is to ensure product quality. The PAT-enabled control system of a manufacturing process provides the capability to determine the current status of the process and drive the process to ensure the output material has the desired quality characteristics. The control system should be able to respond to process variations in a timely manner, providing corrections that ensure that the process follows the desired process trajectory to reach the desired outcome. PAT-enabled control systems may use process models based on first principles understanding or empirical models derived from experimental investigations or both. In addition to automated controls, a PAT-enabled control system may include components where there is manual intervention.

1.3 Principles described in this guide may be applied regardless of the complexity or scale of the PAT-enabled control system or whether applied to batch or continuous processing, or both.

1.4 The principles described in this guide are applicable to a PAT-enabled control system and also to its component subsystems. This guide does not cover the requirements for continuous quality verification of the overall process, which are covered in Guide E2537.

1.5 For information on science- and risk-based approaches in the pharmaceutical industry, reference should be made to ICH Q8(R2), ICH Q9, and ICH Q10. For guidance on PAT systems in the pharmaceutical industry, reference should be made to FDA Guidance for Industry—PAT and FDA Guidance for Industry—Process Validation.

1.6 *This standard does not purport to address all of the safety concerns, if any, associated with its use. It is the responsibility of the user of this standard to establish appropriate safety and health practices and determine the applicability of regulatory limitations prior to use.*

2. Referenced Documents

2.1 *ASTM Standards:*[2]

E122 Practice for Calculating Sample Size to Estimate, With Specified Precision, the Average for a Characteristic of a Lot or Process

E2363 Terminology Relating to Process Analytical Technology in the Pharmaceutical Industry

E2476 Guide for Risk Assessment and Risk Control as it Impacts the Design, Development, and Operation of PAT Processes for Pharmaceutical Manufacture

E2500 Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment

E2537 Guide for Application of Continuous Quality Verification to Pharmaceutical and Biopharmaceutical Manufacturing

2.2 *Other Standards:*

ICH Q2(R1) Validation of Analytical Procedures: Text and Methodology[3]

ICH Q8(R2) Pharmaceutical Development[3]

ICH Q9 Risk Management[3]

[1] This guide is under the jurisdiction of ASTM Committee E55 on Manufacture of Pharmaceutical Products and is the direct responsibility of Subcommittee E55.02 on PAT System Implementation and Practice.

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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 Q10 Pharmaceutical Quality System[3]
FDA Guidance for Industry—PAT A Framework for Innovative Pharmaceutical Development, Manufacturing and Quality Assurance[4]
FDA Guidance for Industry—Process Validation General Principles and Practices[4]

3. Terminology

3.1 *Definitions*—See also Terminology E2363 for other PAT terms.

3.1.1 *attribute*, *n*—characteristic or inherent quality or feature. **(E2363)**

3.1.2 *control model*, *n*—procedure or mathematical expression (algorithm) that uses the outputs of the process model combined with any other data inputs required to calculate values for the critical control parameters for the process; it uses input data from the process to generate an actionable command or commands that are issued to the control system.

3.1.2.1 *Discussion*—The control model may define what actions to take when specific attribute values are detected. The control model may be complex or simple, for example, it may be predictive, as in the case of model-based control (MBC) in which it is desired to manage the operation of the process along a particular trajectory; it may be a single proportional integral derivative (PID) loop controller; or it may be anything in between.

3.1.3 *control system*, *n*—system that responds to inputs signals from the process, its associated equipment, other programmable systems or an operator or both, and generates output signals causing the process and its associated equipment to operate in the desired manner.

(Perry's Handbook of Chemical Engineering[5])

3.1.4 *measurement system*, *n*—system of sensors, instruments, and/or analyzers that collects signals generated by passive or active interaction with process material or process equipment and converts those signals into data.

3.1.5 *parameter*, *n*—measureable or quantifiable characteristic of a system or process. **(E2363)**

3.1.6 *process model*, *n*—mathematical expression (algorithm) that uses data from the measurement system(s) (inputs to the process model) to calculate the value of one or more of the process material attributes (outputs from the process model) at the time the measurement was taken.

3.1.6.1 *Discussion*—The process model typically will have to handle sets of orthogonal or nonorthogonal attributes. The mathematical algorithm will ideally represent first-principle understanding of the process being modelled. However, when sufficient first-principles understanding is unavailable, an empirical model may also be used.

3.2 *Acronyms:*

3.2.1 *CCP*—Critical control parameter
3.2.2 *CPP*—Critical process parameter
3.2.3 *CQA*—Critical quality attribute
3.2.4 *CQV*—Continuous quality verification
3.2.5 *FDA*—Food and Drug Administration
3.2.6 *ICH*—International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
3.2.7 *ISA*—International Society of Automation
3.2.8 *LOD*—Limit of detection
3.2.9 *MBC*—Model-based control
3.2.10 *MVA*—Multivariate analysis
3.2.11 *PAT*—Process analytical technology
3.2.12 *PID*—Proportional integral derivative
3.2.13 *PP*—Process parameter
3.2.14 *QA*—Quality attribute

4. Summary of Practice

4.1 To aid reader understanding, a diagram of the data flows in a PAT-enabled control system is shown in Fig. 1.

4.2 Fig. 2 shows how the quality attributes (QAs), noncritical as well as critical, are fed into the control model via the process model. Each process has process parameters (PPs). Based on process understanding, some PPs are held static and others are subject to dynamic adjustment. Some of the PPs directly or indirectly impact critical quality attributes (CQAs) and these PPs are called critical process parameters (CPPs). When the CPPs (which may be fixed or adjustable) are dynamically adjusted as a result of information generated by the process and control models, they are called critical control parameters (CCPs). Revised CCP settings are transmitted in real time to the manufacturing equipment where they change the conditions of manufacture for the product.

5. Significance and Use

5.1 This guide supports the principles of Guide E2500 and extends these principles to the verification of PAT-enabled control systems.

5.2 This guide clarifies what is important for verification of PAT-enabled control systems. Such systems are often complex and require multidisciplinary and cross-functional teams to achieve optimum results. This guide provides a common basis for understanding requirements for all involved disciplines such as control engineering, development, manufacturing, and process validation.

6. Principles To Be Considered for Verification of PAT-Enabled Control Systems

6.1 Verification should be science and risk based. Quality risk management should drive the verification process. Practice E2476 provides additional guidance on risk assessments for PAT systems.

6.2 Verification should use the most efficient and effective method available to achieve the specified results, choosing from, for example, simulation, testing, first principle modeling, or other approaches or combinations of these.

6.3 Verification should cover the range over which the manufacturing process is intended to operate. This will include all those ranges in which it is necessary that the control system will be able to bring the process back into its intended operating range.

[4] Available from Office of Training and Communication, Division of Drug Information, HFD-240, Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, http://www.fda.gov.

[5] *Perry's Handbook of Chemical Engineering*, see BPCS–Basic Process Control System, McGraw Hill, 2007.