Designation: E2629 – 20

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

This standard is issued under the fixed designation E2629; the number immediately following the designation indicates the year of original adoption or, in the case of revision, the year of last revision. A number in parentheses indicates the year of last reapproval. A superscript epsilon (ε) indicates an editorial change since the last revision or reapproval.

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. The intention of this standard is to describe and support the implementation of a PAT enabled Control Strategy, as described in ICH Q8(R2).

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, or for validation of PAT methods, which is covered in Guide E2898.

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, as well as EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use and EU Guideline on Process Validation for Finished Products.

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, health, and environmental practices and determine the applicability of regulatory limitations prior to use.*

1.7 *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]

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

[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 E55.01 on Process Understanding and PAT System Management, 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.

E2500 Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment
E2537 Guide for Application of Continuous Process Verification to Pharmaceutical and Biopharmaceutical Manufacturing
E2898 Guide for Risk-Based Validation of Analytical Methods for PAT Applications

2.2 *Regulatory Guidance and Other Documents:*
ICH Q2(R1) Validation of Analytical Procedures: Text and Methodology[3]
ICH Q8(R2) Pharmaceutical Development[3]
ICH Q9 Risk Management[3]
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]
EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use Annex 15: Qualification and Validation[5]
EU Guideline on Process Validation for Finished Products [5]

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[6]

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. The diagram shows how process and control models can be used in a closed loop control paradigm (with decisions being made based on action limits set in the control model) but also for feed-forward control to downstream process steps/operations.

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)

[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 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] Available from the European Commission (European Union (EU)), https://ec.europa.eu.

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

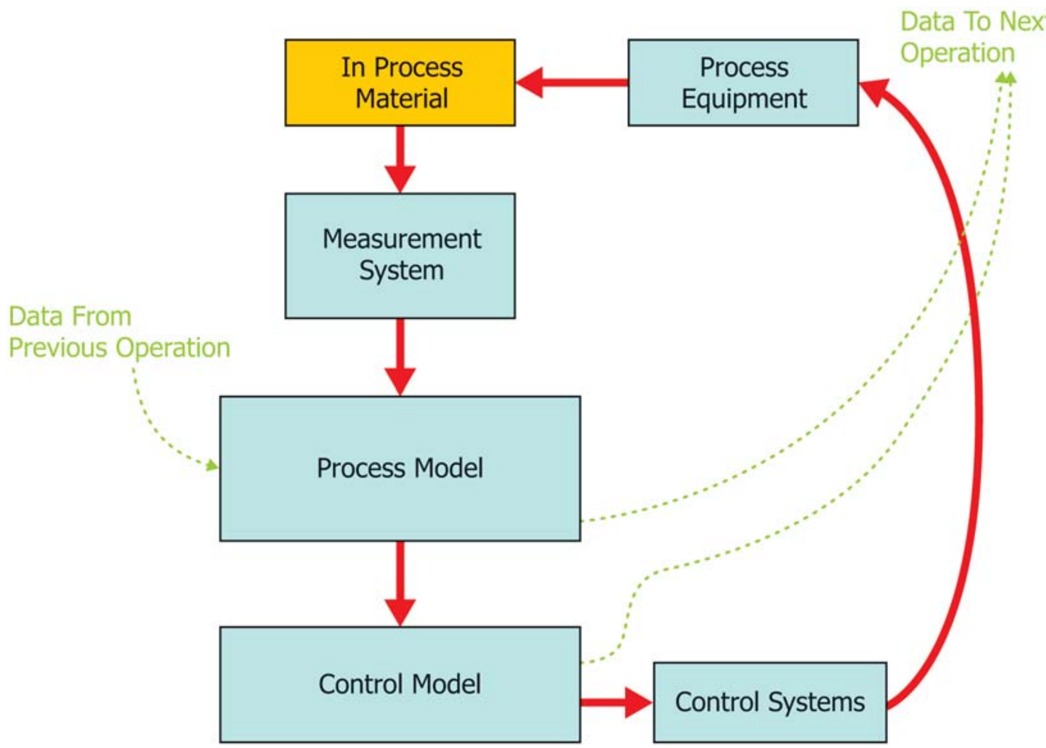

FIG. 1 Data Flows for a PAT-Enabled Control System

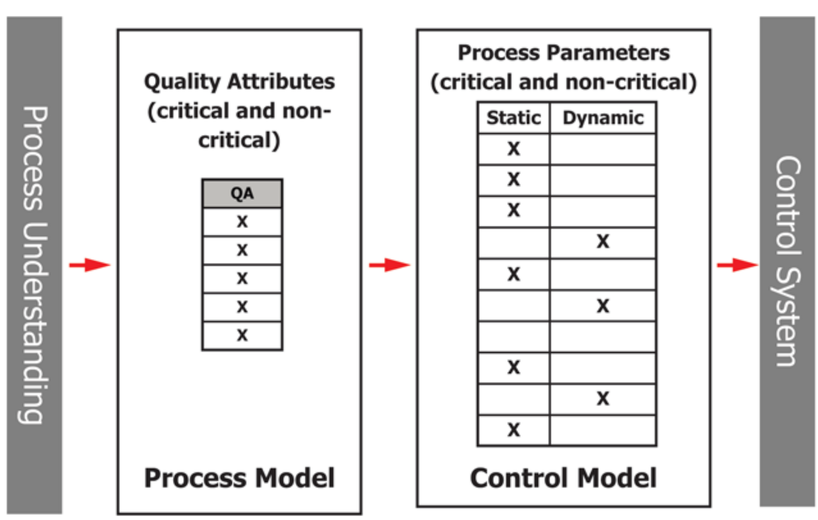

FIG. 2 Relationship Between Quality Attributes and the Control System

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.

4.3 *Control Strategy:*

4.3.1 The control strategy should be designed to control the quality of the product in response to potential variations in the process, equipment conditions, incoming raw materials, or environmental factors over time. Control strategy implementations generally can be categorized into three types:[7]

4.3.1.1 *Level 1: Quality Assurance by Means of Application of Dynamic or Adaptive Process Control System:*

(1) A Level 1 control strategy utilizes Dynamic or Adaptive Process Control System to monitor and control the quality attributes of materials in real-time.

[7] "Modernizing Pharmaceutical Manufacturing: From Batch to Continuous Production," *Journal of Pharmaceutical Innovation*, Vol 10, No 3, September 2015.