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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]

ICH Q10 Pharmaceutical Quality System[3]

[1] This guide is under the jurisdiction of ASTM Committee E55 on Manufacture of Pharmaceutical Products and is the direct responsibility of Subcommittee E55.01 on 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.

[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.

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:*

3.1.1 See also Terminology E2363 for other PAT terms.

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

3.1.3 *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.

3.1.3.1 *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.

3.1.4 *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])

3.1.5 *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.

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

3.1.7 *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.

3.1.7.1 *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.

[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.

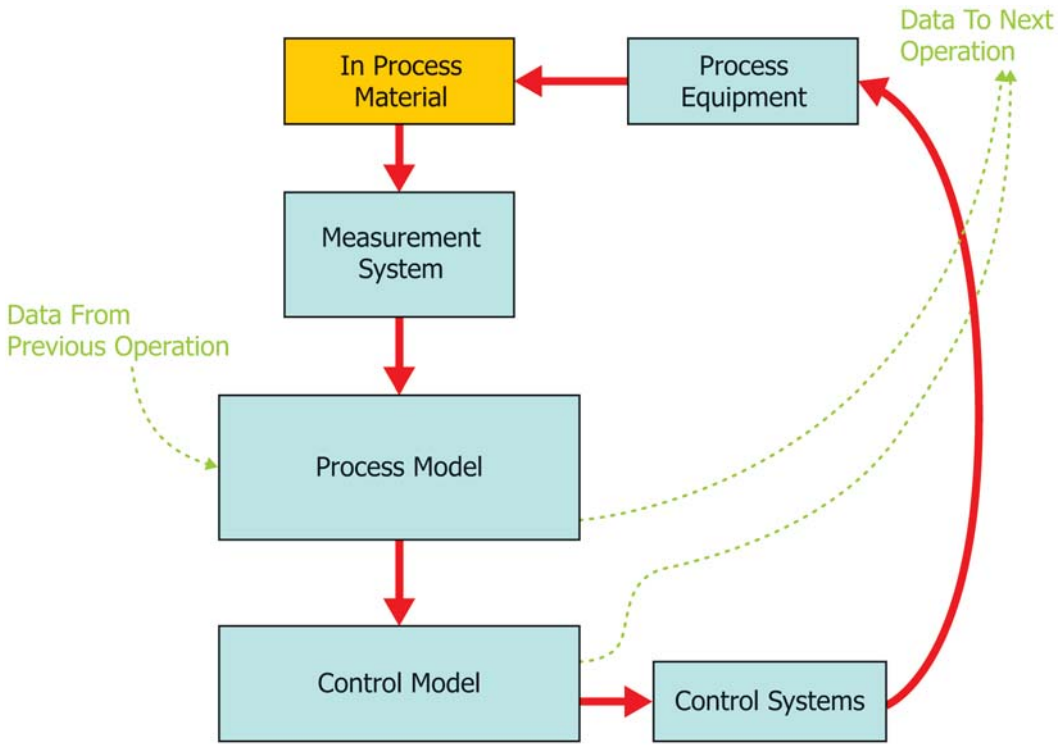

FIG. 1 Data Flows for a PAT-Enabled Control System

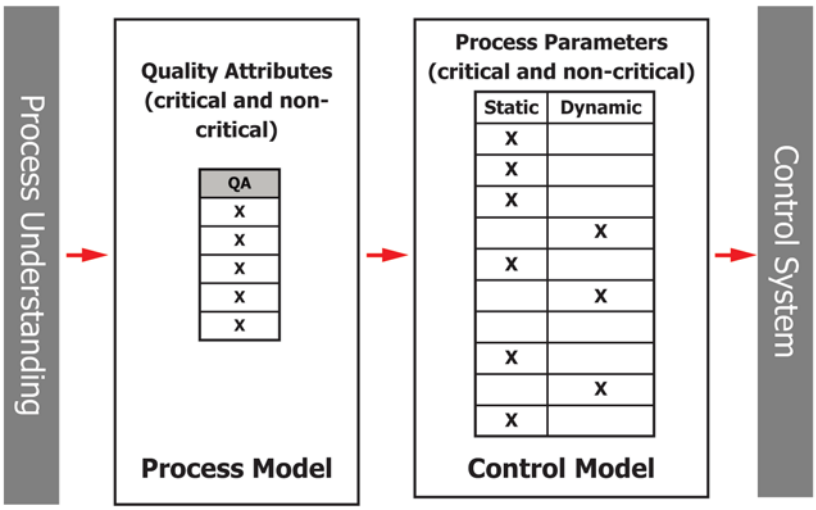

FIG. 2 Relationship between Quality Attributes and the Control System

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.

6.4 Verification of the control systems should always include verification of the system as a whole. It may also include verification of individual system components.

6.5 The verification process should confirm that relevant quality attributes will be controlled concurrently.

6.6 Verification should ensure that the control system is stable throughout the range of operation.

6.7 Each component of the PAT-enabled control system should generate outputs with sufficient frequency, accuracy, and precision to make the necessary level of process control practical, meaningful and value-added.

6.8 Process and control models and the control system should be verified as applicable to the scale of manufacture at which they will be used.

6.9 All stages of the verification should be appropriately demonstrated and clearly documented in accordance with relevant requirements.

7. Verification Process for PAT-Enabled Control Systems

7.1 The verification of PAT-enabled control systems should be science and risk based and normally consists of three stages, as follows. These stages are then expanded further in this section:

7.1.1 Verification planning,

7.1.2 Testing and confirmation, and

7.1.3 Continued verification.

7.2 The extent of verification of PAT-enabled control systems and the detail of documentation will vary on a case-by-case basis. Prior knowledge of the process and experience of the PAT control system when available should be considered and appropriate risk assessment used to help quantify the extent of verification needed.

7.3 *Verification Planning*—The verification plan should describe aspects such as the scope, strategy, stakeholders, and boundaries of the system undergoing verification and if there is a need for process data to be communicated to subsequent unit processes (for example, feed forward). The verification plan includes three important elements: *technical assessment* (see 7.3.1), *sensitivity analysis* (see 7.3.2), and *acceptance criteria* (see 7.3.3).

7.3.1 *Technical Assessment:*

7.3.1.1 Perform a technical assessment of the process control strategy and its capability to deliver the desired final or intermediate product attributes. The purpose of this assessment is to:

(1) Ensure the link to product attributes is understood and clear,

(2) Understand the ranges over which process parameters need to be controlled, and

(3) Ensure that the defined control strategy has been correctly implemented.

7.3.1.2 The following are examples of factors that could be considered for inclusion in the technical assessment:

(1) Meeting the final product attributes or CQAs;

(2) Meeting the intermediate product attributes;

(3) Establishing equipment and operational robustness, repeatability and reproducibility, and accuracy (including process equipment and measurement equipment);

(4) Understanding feedback sensitivity and response speed (damping);

(5) Understanding any external conditions affecting the process and operator interventions;

(6) Variability in quality of the input material to the PAT-controlled process;

(7) Level of understanding in the process and control models;

(8) Novelty and complexity of the overall PAT-enabled control system. Systems that are copies of, use elements of, or are scale-ups of existing control systems may require less testing for verification, provided data are available and the impact of the novelty and complexity on the process can be established; and

(9) Focus the verification testing steps on the elements of the PAT-enabled control system that have the potential to induce the most system variability (such as through a risk assessment process).

7.3.1.3 An example might be if there was significant variability in incoming materials. In this case, more extensive testing of the PAT-enabled controls may be appropriate. Alternatively, when there is a high degree of confidence in the process capability of the upstream steps (for example, they are in a state of statistical process control), then less challenging tests may be appropriate.

7.3.2 *Sensitivity Analysis:*

7.3.2.1 Sensitivity of the process to the variation in the performance of the components of the PAT-enabled control system should be considered and analyzed where and when appropriate. The actual performance of the PAT-enabled control system should be analyzed in relation to these considerations.

7.3.2.2 The PAT-enabled control system typically consists of inputs, processing, and outputs in which the importance of variation in a single component is a function not only of the magnitude of variation but also of the properties of the overall control system. As such, some components may have a greater impact (and, thus, potentially pose greater risk) than others. Components in a system may include, for example:

(1) Measurement equipment:

- Sampling mechanics and systems, and
- Instruments (may generate univariate data, multivariate data, or a combination).

(2) Data preprocessing,

(3) Process model,

(4) Control model,

(5) Process control system,

(6) PAT data management system,

(7) Controls hardware:

- Mechanical,
- Electrical,
- Hydraulic, and
- Pneumatic.

(8) Equipment considerations:

- Equipment scale,
- Systems inertia, and
- Fluid dynamics.

7.3.2.3 *Changing Environmental Conditions*—As part of the sensitivity analysis, stochastic modeling tools such as Monte Carlo simulation may be helpful in understanding how the PAT-enabled control system responds to fluctuations in the inputs when they vary according to certain probability distributions. The varying nature of the inputs, together with the control system sensitivity, can be used to characterize the behavior of the overall system and, thereby, identify areas of high risk as a means of determining the actions designed to reduce the probability of control failure.

7.3.3 *Acceptance Criteria:*

7.3.3.1 *Final Verification Acceptance Criteria*—Once the behavior of the system has been characterized (including the sensitivity and also taking into consideration the possible ranges of the inputs), this information should be factored into the risk analysis for establishing the final acceptance criteria.

The output of the characterization effort will be used to determine sources of high-risk variation in component performance, which, in turn, give rise to risk to product quality.

7.4 *Testing and Confirmation:*

7.4.1 The purpose of testing is to confirm that the PAT-enabled control system delivers what is expected of it for the defined operating range. A typical approach would include testing the measurement system, process model, and control model and then following this by in-situ testing to challenge the PAT-enabled control system. This testing has two general primary components:

7.4.1.1 Testing equivalence to the reference method if applicable through an appropriate statistical equivalence test method.

7.4.1.2 Evaluate the measurement system to determine precision, and repeatability (through analysis of variance gage repeatability and reproducibility [ANOVA gage R&R], for example).

7.4.2 Details are given in 7.4.3 of the various steps involved and an outline of the testing requirements. Note that some of these tests may be combined into a single set of tests with multiple targets.

7.4.3 *Appropriate Measurement System*—Test that the measuring system is installed and calibrated correctly and generates the correct information as follows:

7.4.3.1 Provide scientific data, where necessary, to justify locations where the PAT measurement system is installed;

7.4.3.2 Demonstrate how the measurement system performs to measure (either directly or indirectly) the desired attributes and process parameter(s) and how it is to be calibrated. This can be verified using tools such as hypothesis testing, XBar-R, etc.

7.4.3.3 Verify that the following measurement system characteristics fall within the requirements for the system:

(1) Accuracy,
(2) Dead band/hysteresis,
(3) Dead time (measurement lag),
(4) Repeatability,
(5) Reproducibility,
(6) Stability, and
(7) Capability.

7.4.3.4 For example, it is important that the measurement system performance is verified for the intended use. This could be carried out using the principles of ANOVA gage R&R to ensure the change to be monitored is significantly greater than the demonstrated precision of the measuring system. This step effectively determines that the variance being monitored is above the limit of detection (LOD) of the measurement system (for example, ICH Q2(R1) suggests a signal to noise ratio of 3:1 for the Detection Limit of an analytical method).

7.4.4 *Appropriate Measurement Procedure*—Provide data to show that the installed measurement system and its associated measurement procedure give the appropriate results needed to fulfill fitness for use. This includes data on the appropriate model used to calibrate the measurement systems through the process model and the appropriate conditions for calibration. Note that multivariate analyzers may have unique calibration procedures. This is because they may not directly measure any attribute or parameter that can be traced to a formal independent standard (such as temperature or pH). Hence, the empirical data used to develop the calibration and independent verification of the calibration should be documented. Regardless, the defined calibration requirements should ensure that the entire PAT instrument (measurement system and process model) measures a specific attribute value with a sufficiently low-measurement uncertainty such that the measured values can be used by the control system to effect appropriate control of the process.

7.4.5 *Representative Sampling and Appropriate Sample Size*—Provide data to show that the installed measurement system and sampling method (where applicable) are using sample material from the actual process that is representative of the target material. Scientific and engineering data showing that the sampling mechanics or system or both are correctly placed and the sampling scale and frequency are appropriate should be available. There are various guides available that provide recommendations for calculating appropriate sample size including Practice E122.

7.4.6 *Engineering Data on the Process Model*—Scientific and engineering data should be provided to demonstrate that the specific model or models behave as expected within all areas in which the manufacturing process is intended to operate. In addition, data should be provided to demonstrate that, in the context of the control system, the process model responds to the anticipated rate of change of the process quickly enough to ensure stable operation.

7.4.7 *Engineering Data on the Control Model*—Engineering data should be provided to demonstrate that the specific model or models can, in a timely fashion, drive the process back into its normal operating range from all areas in which the manufacturing process is intended to operate.

7.4.8 *General Engineering Data on the Control System*—The process control strategy should be documented. The understanding of how to regulate the process to the desired set points should be documented. This shows how the control system will operate to vary the determined parameters and that the control model can control the selected system parameters and process material quality attributes. Examples are control of temperature, pressure, or flow to either static or dynamic set points and within predetermined tolerances.

7.4.9 Control system testing should demonstrate not only that it is stable, but also that it has acceptable steady-state and dynamic performance when responding to changes in all areas in which the manufacturing process is intended to operate. Acceptable performance is defined and documented appropriately. It may be based upon standard stable responses but may equally be based upon dynamic instability, which is integrated into the strategy and used to improve control and dynamic response of the system.

7.4.10 The overall PAT system should be tested in situ by carrying out challenges to show how the individual systems are linked together so that they operate as a whole and will control the overall manufacturing process (for example, in real time.) This data should consist of controlled and documented engineering runs to prove that the system being evaluated works

and performs as specified. In-situ testing should challenge the system using the following techniques:

7.4.10.1 *Set Point Following*—Change the set point and verify the control system settling time, overshoot, and steady-state error are within limits.

7.4.10.2 *Process Disturbance*—Disturb the system by varying the parameters, process attributes, and input materials, or combination thereof, towards the boundaries of the intended range to confirm the system is capable of controlling the desired attribute with a high degree of confidence. Verify settling time, overshoot, and steady-state error are within limits. These disturbance tests may be of two types:

- Disturb the system and do not return it to its normal position. Obtain confirmation that the control system automatically brings the process back under control.
- Disturb the system for a short time then return it to its normal position. Obtain confirmation that control remains and that, for example, no undesirable oscillations are set up.

(1) An example of such a test would be forcing a change in a temperature and observing the resulting system changes, such as a change in airflow, that are made to maintain control of a particular attribute.

(2) In designing these disturbance tests, it is important to assess that the perturbations are within the range of the process and control models to prevent possible second-order effects, such as undesirable oscillations. It is also important that, in the tests, the expected variations in local operating or environmental conditions are taken into account, for example, at a location where large variations in relative humidity of atmospheric air are expected, the tests should cover the full range of relative humidities.

(3) The response of the system to the perturbation should be to bring the system back to the target values for that stage of the process in a smooth and timely manner.

7.4.10.3 *Discrete Control*—Run the process within its normal range and verify the control system attempts to take proper action at the appropriate times.

7.4.11 Having done the disturbance testing, any adjustments arising from the testing should be carried out and the disturbance tests repeated, if necessary. The testing and final configuration of the PAT-enabled control system and its process and control models should be fully documented.

7.4.12 *Confirmation*—As a final confirmation, the process should be run over time and samples collected to demonstrate good correlation between predicted attributes from the process model and actual data.

7.4.13 This approach is consistent with Guide E2537, which may provide techniques and procedures upon which a continuous verification program could be built.

7.5 *Continued Verification of the PAT-Enabled Control System*—During this stage, ongoing assurance is gained that the PAT-enabled control system continues to perform as intended during routine commercial manufacture. Details of how to carry out continued verification of the PAT-enabled control system are not covered within this guide, but this activity would normally be a supporting part of continuous quality verification of the overall process—see Guide E2537.

8. Keywords

8.1 controls; data management; process analytical technology; process equipment; risk assessment