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Standard Guide for Risk-Based Validation of Analytical Methods for PAT Applications[1]

This standard is issued under the fixed designation E2898; 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 provides an overview to the risk-based validation of process analytical methods under a process analytical technology (PAT) paradigm for pharmaceuticals and biopharmaceuticals and as such includes guidance on assessing risk to product quality from inappropriate method validation.

1.2 This guide builds on existing standards on the topic of validation concentrating on applying such standards to analytical methods for on-line analysis. In particular, it addresses the validation of at-line, on-line, or in-line PAT measurements and covers both drug substance and drug product (DP) measurements.

1.3 The definitions of International Council for Harmonisation (ICH) validation parameters (such as specificity, precision, repeatability, etc.) apply; however, the method of demonstrating the validation parameters may vary from that described in ICH and is discussed.

1.4 As consistent with the U.S. Food and Drug Administration (FDA) process validation guidance, this document also briefly covers ongoing assurance that the method remains in a validated state during routine use.

1.5 Equipment and instrument qualification are out of the scope of this guide but will be referenced as inputs to validation of analytical methods for PAT applications.

1.6 The validation of multivariate prediction models is out of scope but will be referenced as inputs to validation of analytical methods for PAT applications.

1.6.1 The validation of any analytical model used in the PAT method is essential to the validation of the PAT method but, the details of the model validation process is out of scope. See term *model validation*, 3.1.7.

1.7 Microbiological methods are out of scope.

1.8 *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.*

1.9 *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]

D3764 Practice for Validation of the Performance of Process Stream Analyzer Systems

D6122 Practice for Validation of the Performance of Multivariate Online, At-Line, Field and Laboratory Infrared Spectrophotometer, and Raman Spectrometer Based Analyzer Systems

E1655 Practices for Infrared Multivariate Quantitative Analysis

E1790 Practice for Near Infrared Qualitative Analysis

E2056 Practice for Qualifying Spectrometers and Spectrophotometers for Use in Multivariate Analyses, Calibrated Using Surrogate Mixtures

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

E2617 Practice for Validation of Empirically Derived Multivariate Calibrations

E2629 Guide for Verification of Process Analytical Technology (PAT) Enabled Control Systems

E2656 Practice for Real-time Release Testing of Pharmaceutical Water for the Total Organic Carbon Attribute

E2891 Guide for Multivariate Data Analysis in Pharmaceutical Development and Manufacturing Applications

[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 E55.13 on Process Evaluation and Control.

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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.

2.2 *ICH Standards:*[3]

ICH Quality Implementation Working Group Points to Consider (R2) ICH-Endorsed Guide for ICH Q8/Q9/Q10 Implementation dated 6 December 2011

Q2(R1) Guidance on Validation of Analytical Procedures: Text and Methodology

Q7 Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients

Q9 Quality Risk

2.3 *Other Standards:*

ASME BPE2019 BioProcessing Equipment Standard[4]

FDA Guidance for Industry Process Validation: General Principles and Practices[5]

ISO 14971 Medical Devices—Application of Risk Management to Medical Devices[6]

ISO 15839 Water Quality—On-line Sensors/Analysing Equipment for Water—Specifications and Performance Tests[6]

ISO/IEC Guide 51 Safety Aspects—Guidelines for Their Inclusion in Standards[6]

PAT A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance, Guidance for Industry, September 2004[5]

USP Acoustic Emission <1005> [7]

3. Terminology

3.1 *Definitions:*

3.1.1 *acceptance criteria, n*—criteria that a system or component shall satisfy to be accepted by a user or other authorized entity.

3.1.2 *at-line measurements, n*—measurement in which the sample is removed, isolated from, and analyzed in close proximity to the process stream.

3.1.3 *categorical data, n*—measurement output that has distinct and predetermined output options (for example, pass/fail, 1/0, red/yellow/green, and on/off) and is typically nonnumeric in nature.

3.1.4 *continuous data, n*—numerical information or output having any values within a given range.

3.1.5 *discrete data, n*—numerical information for which a limited set of values are allowed within a given range.

3.1.6 *in-line measurements, n*—measurement in which the sample is not removed from the process stream, which may be either invasive or noninvasive.

3.1.7 *model validation, n*—the process of testing a calibration model with validation samples to determine bias between the estimates from the model and the reference method, and to test the agreement between estimates made with the model and the reference method as defined in Guide E2891.

3.1.8 *off-line measurements, n*—measurement in which the sample is removed or isolated from the immediate manufacturing process stream, and analyzed in an area remote from the manufacturing process.

3.1.9 *on-line measurements, n*—measurement in which the sample is diverted from the manufacturing process and may be returned to the process stream.

3.1.10 *process analytical technology (PAT) application, n*—the installation/utilization of a measurement system, for designing, analyzing, and controlling manufacturing through timely measurements (that is, during processing) of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality. **PAT**

3.1.11 *qualification, n*—action of proving and documenting that equipment or ancillary systems are properly installed, work correctly, and are fit for their intended purpose.

3.1.11.1 *Discussion*—Qualification is part of validation, but the individual qualification steps alone do not constitute process validation. **FDA/ICH Q7A**

3.1.12 *qualitative, adj*—type of method whereby a categorical outcome (such as pass/fail) is generated for the attribute or parameter measured.

3.1.12.1 *Discussion*—The method output may be descriptive rather than numerical.

3.1.13 *quantitative, adj*—type of method whereby a numerical value or result is generated for the attribute or parameter measured.

3.1.14 *reference sample, n*—representative substance of established quality used as a reference standard for the method validation.

3.1.14.1 *Discussion*—The reference sample may be a reference standard (primary or secondary) and may be commercial or development material for which the value of its relevant parameter or attribute has been established. **E1655**

3.1.15 *risk, n*—combination of the probability of occurrence of harm and the severity of that harm. **ISO/IEC Guide 51, ICH Q9**

3.1.16 *risk analysis, n*—the estimation of the risk associated with the identified hazard. **ICH Q9**

3.1.17 *risk assessment, n*—a systematic process of organizing information to support a risk decision to be made within a risk management process. Consisting of identification hazards and the analysis and evaluation of risks associated with exposure to those hazards. **ICH Q9, ISO 14971**

3.1.18 *verification, n*—systematic approach to demonstrate that manufacturing systems, acting singly or in combination, are fit for intended use, have been properly installed, and are operating correctly.

3.1.18.1 *Discussion*—This is an umbrella term that encompasses all types of approaches to assuring systems are fit for use such as qualification, commissioning and qualification,

[3] Available from International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), ICH Secretariat, Route de Pré-Bois, 20, P.O Box 1894, 1215 Geneva, Switzerland, https://www.ich.org.

[4] Available from American Society of Mechanical Engineers (ASME), ASME International Headquarters, Two Park Ave., New York, NY 10016-5990, http://www.asme.org.

[5] Available from U.S. Food and Drug Administration (FDA), 10903 New Hampshire Ave., Silver Spring, MD 20993, http://www.fda.gov.

[6] Available from International Organization for Standardization (ISO), ISO Central Secretariat, Chemin de Blandonnet 8, CP 401, 1214 Vernier, Geneva, Switzerland, https://www.iso.org.

[7] Available from U.S. Pharmacopeial Convention (USP), 12601 Twinbrook Pkwy., Rockville, MD 20852-1790, http://www.usp.org.

verification, system validation, or other validation. There is recognition that the word verification is used in conjunction with validating process systems and that the word validation is used for analytical methods.

3.2 *Acronyms:*

3.2.1 *ICH*—International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

3.2.2 *LOD*—limit of detection

3.2.3 *LOQ*—limit of quantification

3.2.4 *PAT*—process analytical technology

3.2.5 *RTRT* —real time release testing

3.2.6 *DOE*—design of experiments

4. Significance and Use

4.1 This guide supports the principles of Guide E2500 and extends these principles to validation of analytical methods for PAT applications. The ongoing process of method validation is graphically represented in Fig. 1, which shows the life cycle of the validation of analytical methods for PAT applications. Prerequisites for validation are the identification of the measurement requirements and development of a method to meet those requirements.

4.2 The method risk assessment also takes into account the stage in the product life cycle at which the measurements are being made and how the resulting data will be used. The integration of these considerations in the risk assessment facilitates the determination of the level of validation necessary to ensure that the method is fit for purpose.

4.3 Changes may occur during the product life cycle necessitating identification of changes to the measurement requirements and method update and revalidation. Procedures should be established to evaluate the continued suitability of the process analytical method and to make appropriate recommendations to update the process analytical method for the intended use during the product life cycle.

4.4 Additional informative examples can be found in Practices D3764, D6122, E1655, E1790, E2056, E2617, and E2656; and Guide E2891 that address validation of methods and models. Other useful standards include ASME BPE2019, ISO 14971, ISO 15839, and USP Acoustic Emission <1005>.

5. Significance and Use

5.1 Guidance documents for the validation of off-line, laboratory-based analytical methods frequently have requirements that cannot be satisfied when applied to at-line, on-line, and in-line analytical methods for PAT applications. This guide provides guidance for the validation of at-line, on-line, or in-line analytical methods for PAT applications. Additionally, this guidance should be used in conjunction with Guide E2629 when the PAT measurement is an integral part of a process control system.

5.2 The documentation required for validation necessary to demonstrate that the analytical method is fit for purpose for the intended application at the stage of the product life cycle may be determined by assessing the risks to quality. The documentation requirements for validation is determined by risk assessment and will depend on the intended use. For example, a process analytical method used during the development stage for research purposes, may be important for pharmaceutical innovation and pharmaceutical research and development, but may not carry the same level of validation documentation requirements compared to a method that is being used during the commercial manufacturing stage of the product life cycle to support quality decisions about the product. Similarly, the documentation requirements for validation of a method that is being used during the manufacturing stage of the product life cycle to support the quality decision about the product may differ from those listed in ICH Q2(R1). These differences in documentation requirements for validation will depend on the level of criticality of the risk of the application.

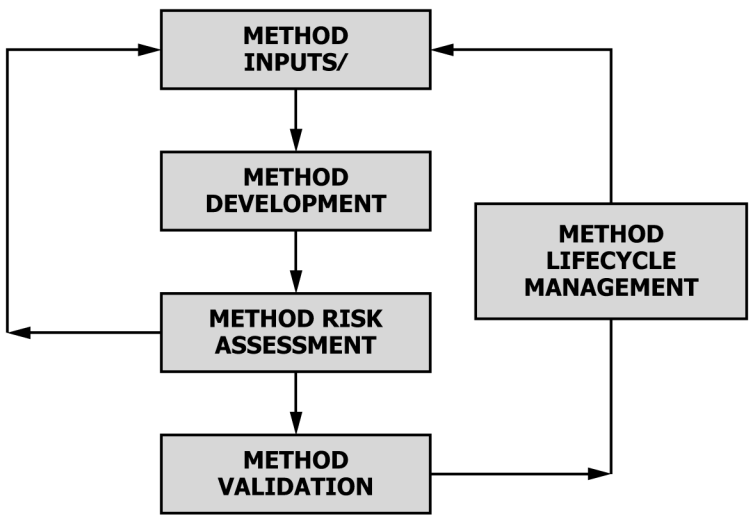

FIG. 1 Life Cycle for the Validation of Analytical Method for PAT Applications

6. Procedure

6.1 *Inputs to Validation:*

6.1.1 There are a number of inputs to the risk assessment process such as establishing the measurement need, determining the intended purpose, establishing the measurement system, establishing the measurement interface, measurement location, measurement frequency, validation of any analytical models used in the method, and developing the process analytical method.

6.1.2 *Defining the Intended Purpose of the Application*—This includes the analytical target profile, the application and the level of the risk associated with the use of the specific application. This is defined well in the ICH Quality Implementation Working Group Points to Consider (R2). While the ICH guide discusses levels of as they apply to modeling, the same principle applies to the validation of analytical methods for PAT applications.

6.1.2.1 *Low-Impact Applications*—These are applications that are typically used to support product and process development. This level would include activities of low risk such as gathering information on a process, method feasibility, process and formulation optimization, and other similar activities where no control decisions are made.

6.1.2.2 *Medium-Impact Applications*—Included in this category are applications that assure quality, but are not the only measure of product quality. Examples of this may include many development measurements that are used to establish design space and other in process measurements of CQAs that may have another release test for the attribute. Other examples may include measurements that can be used for control decisions but the measurement is verified downstream, and the process data is not used specifically for release.

6.1.2.3 *High Impact Applications*—These are applications that fall into the measurement of product quality category such as control decisions for Real Time Release Testing (RTRT). This is the application that incorporates the measurement to insure product quality by control of the process or is a substitute for a specification test such as product assay or is replacement for dissolution.

(1) It is important to recognize that the level of impact of the applications is categorized by low, medium, and high for ease of documentation and practical purpose. In reality, situation may arise that the initial categorization of the impact level of the analytical method of PAT application may change, due to new information available or situation change which leads to risk categorization change.

6.1.3 *Establishing the PAT Measurement System*—Measurement system qualification is out of scope for this guide and is referenced here as an input. The extent of the hardware and software qualifications is linked to the purpose of the application. Refer to Guide E2500, ASME BPE2019, and other appropriate standards for process qualification and validation reference material. The qualification should be summarized, documented, and approved before initiating the validation process.

6.1.4 *Planning and Development of the Analytical Method for PAT Applications*—The process analytical method development document should state the need and purpose of the method to be developed as previously defined in 6.1.2 including sampling and instrument interface development considerations. Aspects that should be considered and documented include:

6.1.4.1 Attributes or parameters to be measured.

6.1.4.2 Measurement mode—at-line, on-line, or in-line.

6.1.4.3 Choice of the instruments and the interface.

6.1.4.4 Sampling requirement for the measurement (sampling should be handled in accordance with scientifically justified and representative analytical sampling procedures and may evolve throughout the method life cycle):

- Static or dynamic sampling,
- Frequency of sampling and speed at which the measurement result is obtained,
- Number of sampling points,
- Location of sampling points, and
- Size/amount of the batch to be sampled (scientifically justified and representative analytical sampling plan should be developed).

(1) It should be recognized that representative sampling could be challenging, especially for dynamic sampling under process environment. Noise from dynamic process stream, possible artifacts from material which is stagnate on the measurement interface or measuring pathway, and measurement instrument's signal to noise ratio, etc., should be taken into consideration when developing dynamic sampling strategy.

6.1.4.5 Determination/understanding of the sources of process variation and measurement robustness requirements.

6.1.4.6 Fit for purpose in terms of precision and accuracy.

6.1.5 *Method Output Requirements:*

6.1.5.1 Qualitative versus quantitative;

6.1.5.2 Discrete, continuous, or categorical;

6.1.5.3 Trajectory/trending versus single value; and

6.1.5.4 Understanding of process and environmental conditions.

6.1.6 *Risk Assessment*—A risk assessment should be performed to identify the focus and extent of validation documentation necessary considering the risks associated with the equipment, interface, and method itself in relation to the intended use of the measurement information obtained from the method. Risks should be considered in relation to the potential impact on product quality.

6.1.6.1 The documentation requirement for validation of an analytical method for PAT applications will frequently increase during the product life cycle, especially during the product and process development stage until the product is commercialized. For example, little or no validation is required when the method application is of a low level such as gathering data for information purposes, where as much more extensive documentation may be required to demonstrate validation of high level applications during the development stage of the life cycle. During the development stage of the product life cycle, the impact to product quality will typically come from the fact that measurement data generated by the method may be used to make decisions concerning the design of the product and manufacturing process, the establishment of an effective control strategy, acceptance criteria in specifications, and so forth.