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

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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 API and Drug Product (DP) measurements.

1.3 The definitions of International Conference on Harmonization (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.

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

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, and Laboratory Infrared Spectrophotometer 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

[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.

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
2.2 *ICH Standards:*[3]
Q2(R1) Guidance on Validation of Analytical Procedures: Text and Methodology
Q7 Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients
Q9 Quality Risk
ICH Quality Implementation Working Group Points to Consider (R2) ICH-Endorsed Guide for ICH Q8/Q9/Q10 Implementation dated 6 December 2011
2.3 *Other Standards:*
ASME BPE2009 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]
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 *off-line measurements, n*—measurement in which the sample is removed, isolated from, and analyzed in an area remote from the manufacturing process.

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

3.1.9 *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.

3.1.10 *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] 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 American Society of Mechanical Engineers (ASME), ASME International Headquarters, Two Park Ave., New York, NY 10016-5990, http://www.asme.org.
[5] Available from Food and Drug Administration (FDA), 10903 New Hampshire Ave., Silver Spring, MD 20993-0002, http://www.fda.gov.
[6] Available from International Organization for Standardization (ISO), 1, ch. de la Voie-Creuse, CP 56, CH-1211 Geneva 20, Switzerland, http://www.iso.org.
[7] Available from U.S. Pharmacopeia (USP), 12601 Twinbrook Pkwy., Rockville, MD 20852-1790, http://www.usp.org.

3.1.10.1 *Discussion*—

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

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

3.1.11.1 *Discussion*—

The method output may be descriptive rather than numerical.

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

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

3.1.13.1 *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**

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

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

3.1.16 *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**

3.1.17 *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.

3.1.17.1 *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, 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 Conference on Harmonization of Technical Requirements for Registration of 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

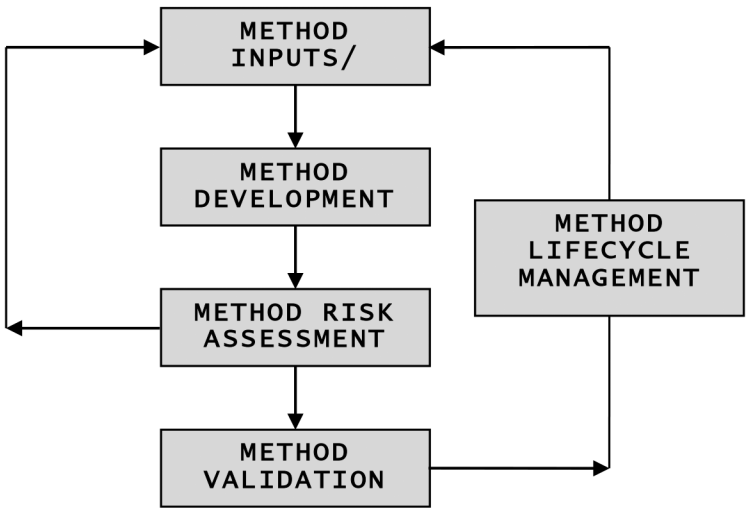

FIG. 1 Life Cycle for the Validation of Analytical Method for PAT Applications

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.

4.4 Additional informative examples can be found in Practices D3764, D6122, E1655, E1790, E2056, E2617~~and~~, ~~E2617~~and E2656 that address validation of methods and models. Other useful standards include ASME BPE2009, 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 have little or no requirements for documenting validation 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.

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, and developing the process analytical method.

6.1.2 *Defining the Intended Purpose of the Application*—This includes the design intent of 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.

6.1.2.2 *Medium-Impact Applications*—Included in this category are applications that assure quality, but are not measurement 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, but the data is not used specifically for release.

6.1.2.3 *High Impact Applications*—These are applications that fall into the Real Time Release Testing (RTRT) category. 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.

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 BPE2009, 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):