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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

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

[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.

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.

3.1.10.1 *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 validation of analytical methods for PAT applications.

[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.

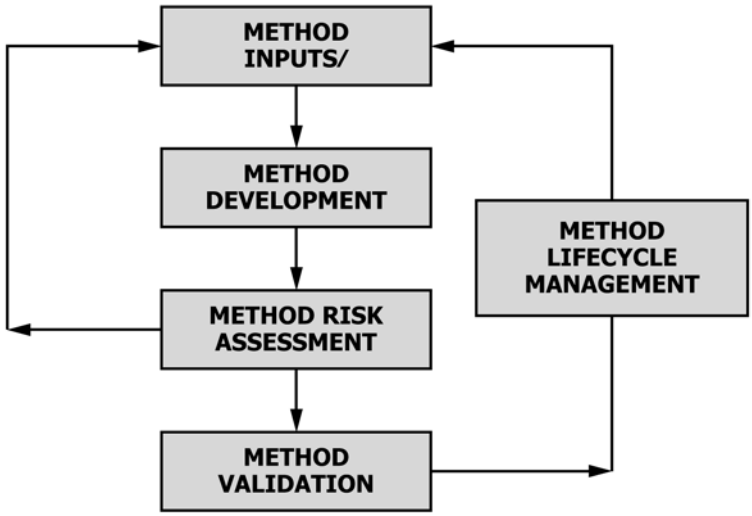

FIG. 1 Life Cycle for the Validation of Analytical Method for PAT Applications

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 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):

(1) Static or dynamic sampling,

(2) Frequency of sampling and speed at which the measurement result is obtained,

(3) Number of sampling points,

(4) Location of sampling points, and

(5) Size/amount of the batch to be sampled (scientifically justified and representative analytical sampling plan should be developed).

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

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 Process conditions and environmental considerations.

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. In the implementation and commercial stage of the product life cycle, documentation of the risk assessment and rationals for the conclusions reached can help knowledge management of the analytical method throughout the life cycle, especially during method transfer. This can also promote understanding of the validation approach when audited by an external organization such as a regulatory agency. Understanding of the criticality of the application and the range over which the method has been shown to be applicable should always drive the design of the validation documentation.

6.1.6.2 To the extent that future requirements for the method can be anticipated, the validation plan may be designed so that evidence is generated to demonstrate that the method is suitable for its intended application at each point in the life cycle. For the efficient use of resources, the plan will ideally be structured in such a way that validation documentation for a new method purpose can build on earlier studies. The principles, tools, and approaches described in ICH Q9 and Guide E2476 can help in the design and execution of this risk assessment.

6.1.6.3 *Assess Validation Parameters for Current Method*—For analytical methods for PAT applications, there may be situations in which validation parameters listed in the guidance document ICH Q2(R1), namely, accuracy, precision, repeatability, intermediate precision, specificity, detection limit, quantitation limit, linearity, range, and robustness may not be applicable. Some of these characteristics are impractical to evaluate and some may not be necessary for validation of the process analytical method for a particular method purpose. An assessment of these validation parameters should be included in the validation plan detailing how they should be evaluated or a rationale should be included as to why they are not to be included. This assessment should include consideration of the following:

(1) Applicability for the method purpose,

(2) Ability to conduct primary sampling,

(3) Whether the act of sampling may change the sample in question,

(4) Practicality of manufacturing representative samples in suitable quantities required for calibration and validation purposes, and

(5) Practicality of validation samples to cover the expected variability exhibited in the manufacturing materials and process that may affect the application of the method.

6.2 *Validation Process:*

6.2.1 The validation process should be planned and documented before execution and should consider elements such as the validation pathway, sampling, process impact, validation parameters, and the validation life cycle management. Documentation requirements can be linked directly to the criticality of the application.

6.2.1.1 *Documentation for Low Impact Applications*—The requirements here should be minimal and could be covered by a discussion of design intent of the application.

6.2.1.2 *Documentation for Medium Impact Applications*—The level of documentation for this may include such elements as the design intent, documentation of the method development, method assumptions, reasons for the method collection, processing and modeling decisions, and statistical analysis of the method.

6.2.1.3 *Documentation for High Impact Applications*—This is the highest level of documentation for the application. The intended purpose of the rest of this document will be to address this level of validation, and the issues that need to be considered and documented for applications with this highest level of criticality.

6.2.2 *Validation Pathway*—The interface of the PAT application will have been determined during method development; however, it is important to recognize that the process analytical interface to the production line may directly impact the ability and pathway to conduct validation and documentation. Four potential validation pathways are outlined in Table 1.

6.2.2.1 Laboratory-based analytical methods for PAT applications such as those with an intended off-line or at-line measurement mode (Validation Pathway 1; Column 1 in Table 1) can largely follow traditional means (whereby appropriate number of representative samples can be evaluated by the new process analytical method) with appropriate reference analysis as needed.

6.2.2.2 The dynamic nature of the sample measurement and the environmental conditions during measurement (temperature, pressure, and so forth) impact on-line and in-line methods and may provide various options for the pathway for validation. Three typical pathways for validation of on-line and in-line measurement interfaces are described in Table 1 in which validation measurement may occur:

(1) Off-line/at-line,

(2) On-line/in-line at smaller or pilot scale, and

(3) On-line/in-line at commercial scale (final installation configuration).

6.2.2.3 Also note that a combination of pathways may be used such as applying Validation Pathway 3 or 4 with additional static samples taken for analysis by Validation Pathway 2 to supplement assessment of particular validation parameters.

6.2.2.4 Additional suitable validation steps may be required when the method is transferred to the commercial plant from the laboratory (Validation Pathway 2) or pilot plant (Validation Pathway 3) addressing appropriate validation parameters that may be impacted by the change of scale, process environment, or from static to dynamic sampling.

6.2.3 *Sampling for Method Validation*—While the sampling mode during validation will often mimic that used for routine use of the method, consideration should be given to the need for a different mode during validation, for example, when off-line reference analysis is needed.

6.2.3.1 *Selection of Reference Samples*—The user should consider the availability of samples and the specific PAT application. When validation samples are prepared gravimetrically/volumetrically or commercially available standards are used then reference samples may not be required. The following may be suitable reference samples for validation studies: external reference standards, process samples, or modified process samples (for example, spiked process samples).

6.2.3.2 When samples are removed from a manufacturing process for off-line measurement for monitoring purposes or off-line measurement for calibration purposes, the ability of the samples to continue to represent the manufacturing process at the time sampled/measured shall be taken into consideration. There may be circumstances in which the act of sampling interferes with the manufacturing process (sampling should be restricted/minimized) or samples will change once removed from the manufacturing process. In such cases, this should be addressed as part of the sampling plan to ensure that process analytical method and reference measurements of the same samples are compatible for validation purposes. For example, reactions may be quenched using chemicals and temperature-controlled sample storage may minimize negative effects such as degradation.

TABLE 1 PAT Analytical Test Method Validation Pathways

NOTE 1—Analytical methods for PAT applications with an intended off-line or at-line measurement mode (Validation Pathway 1; Column 1 in Table 1) can largely follow traditional validation approaches (whereby appropriate number of static representative samples can be evaluated by the new process analytical method with appropriate reference analysis as needed). However, the dynamic nature of the sample measurement for on-line and in-line methods may provide various options for the pathway for validation (Validation Pathway 2 to 3; Column 2 to 3 in Table 1).

Validation Pathway	1	2	3	4
Intended Routine PAT Measurement Mode	Off-line/At-line	On-line/In-line	On-line/In-line	On-line/In-line
Validation PAT Measurement Mode	Off-line/At-line	Off-line/At-line	On-line/In-line Pilot Scale	On-line/In-line Commercial Scale
Validation Sampling	Static	Static	Dynamic	Dynamic
Validation Reference Measurement Mode (if necessary)	Off-line/At-line	Off-line/At-line	On-line/In-line or Off-line/At-line	On-line/In-line or Off-line/At-line
Additional Validation on Transfer to On-line/In-line	N/A	Yes	Yes	N/A

6.2.4 *Impact of Process on Validation*—Method validation should consider the effects of operating parameters on the method/measurement such as, but not limited to:

6.2.4.1 The multivariate operational space encompassing process variation.

6.2.4.2 Expected instrument variation.

6.2.4.3 Acceptable changes in product matrix.

6.2.4.4 Changes in the method and measurement system, including:

(1) Changes as a result of aging;

(2) Drift;

(3) Routine maintenance; and

(4) Changes in the composition, source, or supplier of input materials.

6.2.4.5 Environmental factors such as temperature, humidity, and vibration.

6.2.4.6 The method and the measurement system should be validated together as a system. The measurement should be accurate, precise, and robust for typical process conditions. A means to detect excursion of any combination of these factors outside of the validation range(s) should be applied in real time, and the ability to detect excursions outside of the validation range(s) should, itself, be validated.

6.2.5 *Evaluating the Validation Parameters*—The risk assessment should provide scientific rationale or justification for which validation parameters (for example, suitability, detection limit, precision, etc.) are required to validate that the process analytical method is fit for the specific PAT application purpose (as described in 6.1.6.3).

6.2.5.1 The traditional validation parameters used to validate analytical methods can largely be applied to analytical methods for PAT applications. However, in some applications, there may be challenges in applying these directly. When the interpretation or the approach to validate a particular parameter differs from traditional interpretations, explanation as to the scientific reasoning/justification of the approach to assessing the parameter should be given.

6.2.5.2 Analytical methods for PAT applications may be qualitative, including process signature trajectory or incorporate trending approaches.

6.2.5.3 Qualitative methods should be evaluated based on their intended purpose; however, as appropriate, specificity and precision of measurement should be demonstrated.

6.2.5.4 *Specificity*—Specificity will frequently need to be demonstrated for analytical methods for PAT applications. Many analytical methods for PAT applications will examine the analyte of interest within the product matrix and no sample preparation will be used. When specificity is required, it should be demonstrated that the measurement is unequivocally able to assess the analyte in the presence of components that may be expected to be present (for example, background interferences or expected variations in the sample matrix). The method may need chemometrics modeling or statistics to establish specificity. Challenges with the ability to vary sample matrix or present interfering compounds to the measurement system may be experienced. Specificity may be demonstrated off-line for on-line/in-line applications with suitable demonstration that specificity is not impacted by the on-line/in-line process environment. Scientific rationale should be provided to detail how the specificity is demonstrated based on particular nature of the process analytical method as well as the sample interface.

6.2.5.5 *Precision*—Precision measurements will typically need to be performed. It may be challenging for some PAT applications to measure precision at different analyte levels for on-line/in-line interfaces as the different levels may not be typically found in the process environment. As such, precision could be demonstrated across the restricted range of analyte levels as long as the expected impact on precision is considered over a wider range. Precision is typically demonstrated on continuous quantitative data; however, many analytical methods for PAT applications are not quantitative or continuous data. Note that many discrete or categorical output methods do have underlying continuous measurement data available before performing the analysis method. It may be beneficial to apply precision assessment on such underlying continuous raw data rather than on the discrete or categorical method output because the precision of the underlying continuous data impacts the accuracy of discrete or categorical classifications. For quantitative based methods, precision measurements should be based on the final method output rather than raw data.

6.2.5.6 *Reproducibility*—In general, reproducibility is defined as the variation seen as different operators' instruments or laboratories measure the same sample. The ICH definition of reproducibility focuses on interlaboratory transferability, but for the analytical method for PAT applications, validation needs to consider possible variability from these sources. For example, with an at-line system with manual operation, the significance of different operators needs to be considered, whereas, for an automated on-line system, there should be little or no variability as a result of change in operator. In general, reproducibility needs to be determined with regard to all expected sources of variation for the PAT analytical method, including operator, equipment, process, materials, and environment. When methods are transferred, they require assessment of the impact of the transfer. Methods may require updating, maintenance, or further redevelopment as well as revalidation if the method is to be relocated to a different production environment, different measurement system, or different location.

6.2.5.7 *Robustness*—The method itself should be shown to be robust to process variation and expected instrument variation (acceptable changes in product matrix), and the method and measurement system together should be shown to be robust to operate under normal known process conditions. As analytical methods for PAT applications are applied within a specific PAT application and process environment, robustness should be shown for all foreseeable process variation under which the method is intended to function. Considerations for robustness of environmental factors such as temperature variation and vibration are particularly important.

6.2.5.8 *Range and Linearity*—Analytical methods for PAT applications do not necessarily require validation over the extended range typical for laboratory analytical methods. Linearity may pertain to linearity of method response and linearity of method predicted values versus actual values. The

performance of many analytical methods for PAT applications suffers when applied across extended ranges. A method may be developed and validated over a range that covers normal product ranges of the attribute or parameter being measured. Linearity should also be established over the range of the process analytical method. Many analytical methods for PAT applications use advanced regression (including modeling) techniques. Linearity may pertain to linearity of method response and linearity of method predicted values versus actual values. Nonlinear calibrations may be used. The need and mechanism for demonstrating the validity of the linear or nonlinear regression technique should be justified.

6.2.5.9 *Accuracy*—All quantitative methods should have an assessment of accuracy. The acceptance criteria applied to the assessment should relate to the purpose of the application (not all analytical methods for PAT applications will need the same degree of accuracy). The accuracy required within different regions of the operating range may be different. For example, higher accuracy may be desired close to the edges of the operating range to enable better discrimination around the operating boundaries. In such cases, separate scientific rationale and documentation of justification may be developed for separate subregions of the operating range. Classification methods should also assess the ability of the methods to classify data appropriately into discrete or categorical classifications. Trajectory/trending methods should be able to reflect accurately the state of the process at the measurement point. End-point methods should be able to make an end-point determination with sufficient accuracy. Scientific rationale should be used to explain and document the justification for the accuracy assessment based on the process analytical method purpose.

6.2.5.10 *Limit of Detection (LOD) and Limit of Quantification (LOQ)*—LOD and LOQ are often challenging assessments for analytical methods for PAT applications as modification of the sample matrix may impact the capability of the method to perform the analysis (for example, the physical nature of the sample beyond the validated range may differ significantly). It may be determined that assessment of LOD and LOQ does not add value and that scientific demonstration of measurement capability or limitations of the use of the measurement to the established range may be more useful. When quantitative measurements may be taken at or near the LOQ, then the LOQ should be determined. While LOQ is unnecessary for qualitative methods, LOD should be considered.

6.2.5.11 *System Suitability*—For many analytical methods for PAT applications, system suitability is synonymous to measurement system (instrument and sample interface) operation checks. Operation checks may include automated system/vendor system diagnostics or a set of procedures performed to verify suitability of both the instrument and interface. Commercial or vendor-prepared reference standards may also be used to demonstrate that the measurement system is operational (for example, wavelength or transmission standards for spectroscopic methods). System suitability should be documented in a standardized procedure and applied before any measurement during method development, method validation, and later, in routine operation.

6.2.6 *Validation Life-Cycle Management*—Good proactive process validation requires ongoing assurance of validity of the process analytical method throughout the product life cycle. Validation life cycle management encompasses:

6.2.6.1 Ongoing review that the method is still valid,

6.2.6.2 Update of method scope and risk assessment,

6.2.6.3 Method maintenance of predetermined acceptable updates of the method when the method changes post implementation,

6.2.6.4 Method update and revalidation as required during the life cycle of the method, and

6.2.6.5 Appropriate documentation and change control procedures will describe efforts associated with validation life-cycle management of a given analytical method and its associated PAT application.

7. Keywords

7.1 at-line; in-line; in-process measurements; method development; method verification; multivariate modeling; off-line; on-line; particle characterization; PAT; process analytical; process analytical technology; process analytics; process analyzers; qualification; risk assessment; sampling; validation; vibrational spectroscopy