STIMULI TO THE REVISION PROCESS

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Lifecycle Management of Analytical Procedures: Method Development, Procedure Performance Qualification, and Procedure Performance Verification[a]

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ABSTRACT In this *Stimuli* article, the USP Validation and Verification Expert Panel discusses how the modern concept of a lifecycle model, which is based on process validation and described in ICH guidelines Q8, Q9, and Q10, can be applied to analytical procedures. The Expert Panel proposes that the traditional approaches to validation, transfer, and verification should be integrated into the analytical procedure lifecycle process rather than being viewed as separate entities. As a starting point or "predefined objective" according to ICH Q8, the requirements for a measurement of a critical quality attribute are established in the Analytical Target Profile. In alignment with process validation, three stages are proposed: Procedure Design (development and understanding), Procedure Performance Qualification, and Continued Procedure Performance Verification.

INTRODUCTION

Any analytical procedure must be shown to be fit for its intended purpose before use. [NOTE——The term *analytical procedure* used in this *Stimuli* article is interchangeable with the term *method* commonly used in industry and includes steps such as sample preparation, analytical technique, calibration, and definition of the reportable result.]The usual process of demonstrating this suitability in food and drug analytical laboratories takes place by way of a documented validation study and, if required, a verification or transfer process to demonstrate the procedure performs appropriately in the laboratory in which it will be used. The United States Pharmacopeial Convention (USP) has been a strong advocate of this process. General chapter *Validation of Compendial Procedures* <1225>, which was first published in *USP XXI* (1989), served as the foundation for the development of the ICH Q2 Guidance on Validation of Analytical Procedures (*1*). More recently, USP has further led on this topic with the publication of general chapters *Verification of Compendial Procedures* <1226> and *Transfer of Analytical Procedures* <1224> (*Figure 1*).

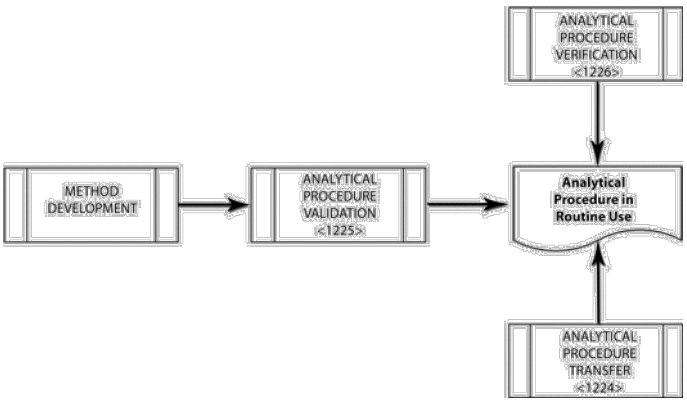

Figure 1. Current typical process for analytical procedures.

The intent of ICH Q2 and <1225> was to provide *guidance* to the industry about how to validate different types of analytical procedures. This guidance was intended to be used in combination with sound scientific judgment to ensure that appropriate experiments applicable to different analytical procedures and situations would be performed on a case-by-case basis. Over time, however, these documents have come to be interpreted as mandatory expectations rather than scientific guidance. Although these practices are successful in many cases, there are opportunities to further refine and improve them.

The ICH and USP documents provide guidance pertaining to procedure suitability as part of the procedure validation exercise (e.g., accuracy, precision, linearity, specificity, etc.), but they do not provide a framework that allows users to reliably understand and control sources of variability. Similar observations were made in the manufacturing process development area, leading to development of the lifecycle management process described in ICH Q8, Q9, and Q10 (and more recently Q11) (*2*–*5*). Taking these ICH documents into consideration, the USP Validation and Verification Expert Panel has reevaluated the current validation, verification, and transfer guidelines for analytical procedures.

The lifecycle concept described in ICH Q8 is adaptable to analytical procedures if we consider an analytical procedure as a process and the output of this process as the reportable result, that is, the value that will be compared to the acceptance criterion. The purpose of applying lifecycle principles to analytical procedures is to holistically align analytical procedure variability with the requirements of the product to be tested and to improve the reliability of the procedure by understanding, reducing, and controlling sources of variability. Enhanced understanding of variables that affect the performance of an analytical procedure provides greater assurance that the quality attributes of the tested product can be reliably assessed. The lifecycle management process provides a framework for defining the criteria for and development of an analytical procedure that meets the acceptance criteria. The procedure then becomes part of a continuous verification cycle to demonstrate that it meets the predefined criteria over the life of the procedure. Implementation throughout the procedure's lifecycle of a change management process that is based on knowledge gained during the procedure's lifetime ensures that the procedure remains fit for its intended use. Key to the general approach is an understanding of overall variability, including variability arising from the manufacturing process as well as the analytical procedure. A focus of USP has been understanding the variability of its reference materials, which are part of the total variability that should be understood, controlled and, where possible, reduced.

In this Stimuli article, the USP Validation and Verification Expert Panel discusses how the modern concept for process validation (6,7), which is based on a lifecycle model, can be applied to analytical procedures (8–11). We propose that the traditional approaches to validation, transfer, and verification should be integrated into the analytical procedure lifecycle process rather than being viewed as separate entities.

The Validation and Verification Expert Panel proposes that the concepts addressed in <1225>, <1226>, and <1224> should be revised and compiled into a single new general information chapter, *Lifecycle Management of Analytical Procedures* <1220> and a new general chapter <220> specifying the basic requirements.

The Validation and Verification Expert Panel seeks reader comments on the contents of this *Stimuli* article.

THE LIFECYCLE APPROACH

Results generated using analytical procedures provide the basis for key decisions regarding compliance with regulatory, compendial, and manufacturing limits. The results are applied against Decision Rules that give a prescription for the acceptance or rejection of a product based on the measurement result, its uncertainty, and acceptance criteria, taking into account the acceptable level of the probability of making a wrong decision (*12,13*).

The adoption of a lifecycle approach to ensure the quality of pharmaceutical products has been extensively discussed during the past several years (*2*–*7*). The concept of Quality by Design (QbD) is understood as a “systematic approach that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management” (ICH Q8). Application of lifecycle management concepts to analytical procedures provides an opportunity to use the knowledge gained from the application of scientific approaches and quality risk management to continual improvement and assurance of data quality.

There should be an effective Quality Management System in place consistent with ICH Q10. The concepts described in ICH Q10 complement current GMPs, thus providing an integrated model for a pharmaceutical or similar quality system. This supports continual improvement across the entire lifecycle of the analytical procedure.

The Analytical Target Profile (ATP), risk management, control strategy, and knowledge management are cornerstone concepts in lifecycle management, which will be discussed in the following sections.

Analytical Target Profile

A fundamental component of the lifecycle approach to analytical procedures is having a predefined objective that stipulates the performance requirements for the analytical procedure. These requirements are derived from the Analytical Target Profile (ATP). See *Figure 2* for some examples.

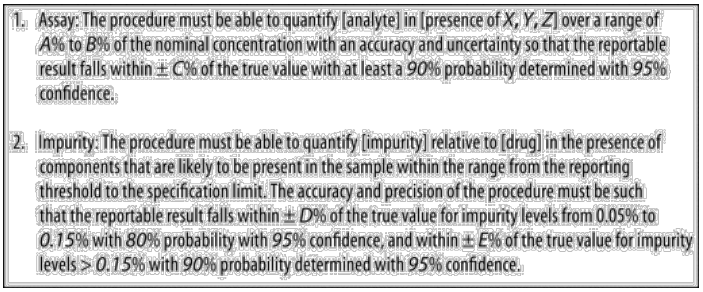

Figure 2. Examples of Potential Analytical Target Profiles. [NOTE—Items in brackets and italics (variables listed as capital letters and numerical values) are placeholders to be replaced by specific items for an ATP.]

The concept of an ATP parallels the concept of a Quality Target Product Profile described and defined in ICH Q8. The ATP defines the requirements for the "product" of the test procedure, which in this case is the reportable result. Criteria defined in the ATP refer to the quality data attributes of the reportable result, i.e., accuracy and measurement uncertainty, which include all sources of variability, including precision. Identifying the output of the analytical procedure as the reportable result provides a target for development and helps to ensure the procedure is developed toward predetermined performance requirements that are directly linked to the quality of the data. In other words, the ATP defines the objective of the test and quality requirements, including the expected level of confidence, for the reportable result that allows the correct conclusion to be drawn regarding the attributes of the material that is being measured. It is essential to reach a high degree of confidence that an analytical procedure will consistently generate reportable results that meet the ATP requirements under all conditions of use and as the material progresses through the lifecycle.

The ATP is based on the understanding of the target measurement uncertainty, which is the maximum uncertainty that the data should have in order to maintain acceptable levels of confidence in data quality. This introduces key performance attributes and changes the way we currently define and evaluate analytical performance characteristics. The ATP serves as a reference point for assessing the fitness of an analytical procedure not only in the development phase but also during all changes within the analytical lifecycle and is not linked to a specific analytical method. It is conceivable that more than one analytical procedure can meet the requirement of an ATP.

Any analytical procedure that has been demonstrated to be capable to generate data that conform to the performance requirements established in the ATP would be regarded as acceptable (*USP* general chapter *Elemental Impurities—Procedures* <233> and *USP Medicines Compendium* general chapter Assessing Validation Parameters for Acceptable Procedures <10>).

Existing procedures also can be evaluated in terms of their ability to meet an ATP. When using a compendial procedure for the first time, an ATP can be derived from monograph specifications, a performance-based monograph, and any existing knowledge of the product.

In assessing new or existing procedures for their capability to meet an ATP, analysts can use statistical methods for analyzing prospectively designed studies (*14*). In the case of existing procedures for which significant historical data are available, statistical procedures for retrospective evaluation of historical data such as stability data, laboratory investigations, check samples/controls, release data, and others are available (*15,16*). The level of variability present in the historical data may trigger additional studies that aim to understand and reduce or eliminate sources of variability and improve the data quality to meet ATP.

Risk Management

A high degree of confidence is needed that the analytical method will generate reportable results that meet the ATP requirements under all conditions of use as the method progresses through the lifecycle. Application of Quality Risk Management (QRM) concepts and tools (ICH Q9) can be valuable in providing a mechanism of achieving this. QRM for analytical procedures can be defined as a systematic process for the assessment, control, communication, and review of risks to the quality of data across the product lifecycle. Process mapping tools and Ishakawa diagrams can be employed to ensure a rigorous approach is used in identifying all potential variables that may affect data quality. The variables should include all aspects of the full analytical procedure (*Figure 3*), i.e., sampling, sample preparation, standards, reagents, facility, and equipment operating conditions.

The identified variables then should be evaluated using appropriate risk-assessment tools and prioritized experimentation to understand, eliminate, or mitigate areas of risk. An approach known as CNX (Control, Noise, Experimental) can help classify all identified variables. A decision can be made concerning which variables should be controlled (C), which are potential noise factors (N), and which should be examined experimentally (X) to determine acceptable ranges. As part of this exercise analysts should provide and document justifications (prior knowledge, scientific rationale, or others) for the assignments made. Risk-analysis tools can then be used to screen experimental (X) variables for DOE studies to minimize the total number of experiments conducted while maximizing knowledge gained. The results of DOE studies then provide justification of the critical variables and their acceptable ranges (from the risk assessment and experimental work), are inputs in the Analytical Control Strategy, and are explicitly specified in the analytical procedure (*Figure 4*).

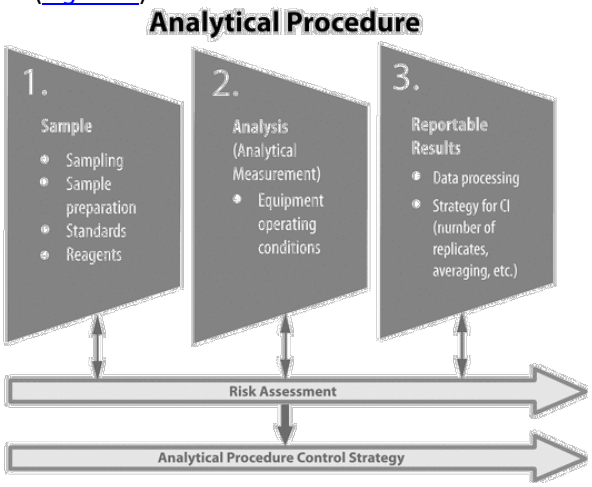

Figure 3. Analytical procedural variables to consider for risk assessment and control strategy.

Figure 4. Quality risk management, control strategy, and knowledge management: how they work together.

Analytical Control Strategy

A well-developed control strategy, i.e., a planned set of controls, is derived from current product and process understanding. The variables and their acceptable ranges (from the risk assessment or experimental work) should be explicitly specified in the procedure. The controls can include variables and aspects related to the sample, sample preparation, standards, reagents, facility, equipment operating conditions, historical experience (prior knowledge), the format of the reportable value (e.g., number of replicates), and frequency of monitoring and control. The Analytical Control Strategy plays a key role in ensuring that the ATP is realized throughout the lifecycle and also should be considered throughout the lifecycle as part of development, continual improvement, and change management.

Different control strategies may be required at different sites. A scientific risk-based approach can be applied to the assessment of a control strategy's suitability across different sites, and quality risk management tools should be used to guide these activities. As an integral part of the laboratory qualification to execute a compendia procedure, the process of quality risk management should be carried out, and the control strategy of the compendia procedure should be verified or expanded in order to ensure that the requirements of the ATP are met.

Knowledge Management

Knowledge management can be defined as a systematic approach to acquiring, analyzing, storing, and disseminating information related to products, manufacturing processes, and components. Knowledge management is an important factor in ensuring the ongoing effectiveness of the control strategy. Knowledge management should include but is not limited to development activities, technology transfer activities to internal sites and contract laboratories, validation studies over the lifecycle of the analytical procedure, and change management activities. The knowledge gathered to develop the method understanding should be collected in a repository and shared as needed to support implementation of the control strategy across sites that use the analytical procedure. Changes and improvements to an analytical procedure should be made with reference to the method knowledge repository, which contains the information from the various stages of the method lifecycle.

We believe that applying a lifecycle approach (*Figure 5*) to analytical procedures will better ensure that quality objectives are met on a consistent basis.

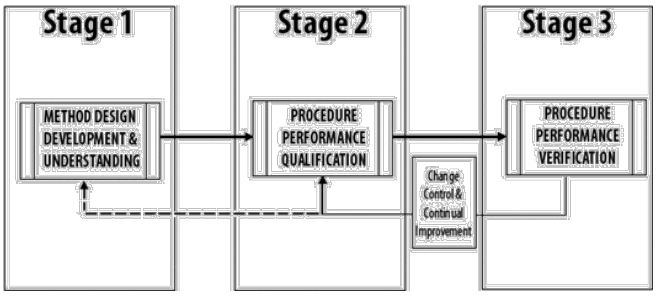

Figure 5. Summary of proposed analytical procedure lifecycle approach.

Lifecycle Stages

In order to provide a holistic approach to controlling an analytical procedure throughout its lifecycle, we propose a three-stage concept that is aligned with current process validation terminology:

- Stage 1—Procedure Design (development and understanding)
- Stage 2—Procedure Performance Qualification
- Stage 3—Continued Procedure Performance Verification.

These steps are illustrated in *Figure 6* and are discussed in the following text.

STAGE 1—PROCEDURE DESIGN

Procedure Development and Understanding (Identify and Study Potential Analytical Variables)

Once the ATP is established and the requirements for data quality (accuracy and uncertainty) of the reportable result are defined, it is the responsibility of the analyst to select an appropriate technology and analytical procedure likely to meet the requirements of the ATP. Consequently, the ATP will be translated into the key performance characteristics of the intended analytical procedure.

The next step is to gain an understanding of how potential sources of variability in the proposed analytical procedure affect the performance characteristics of the procedure. Tools such as process maps and Ishikawa diagrams (fishbones) can be used to provide structure to a brainstorming and information-gathering exercise.

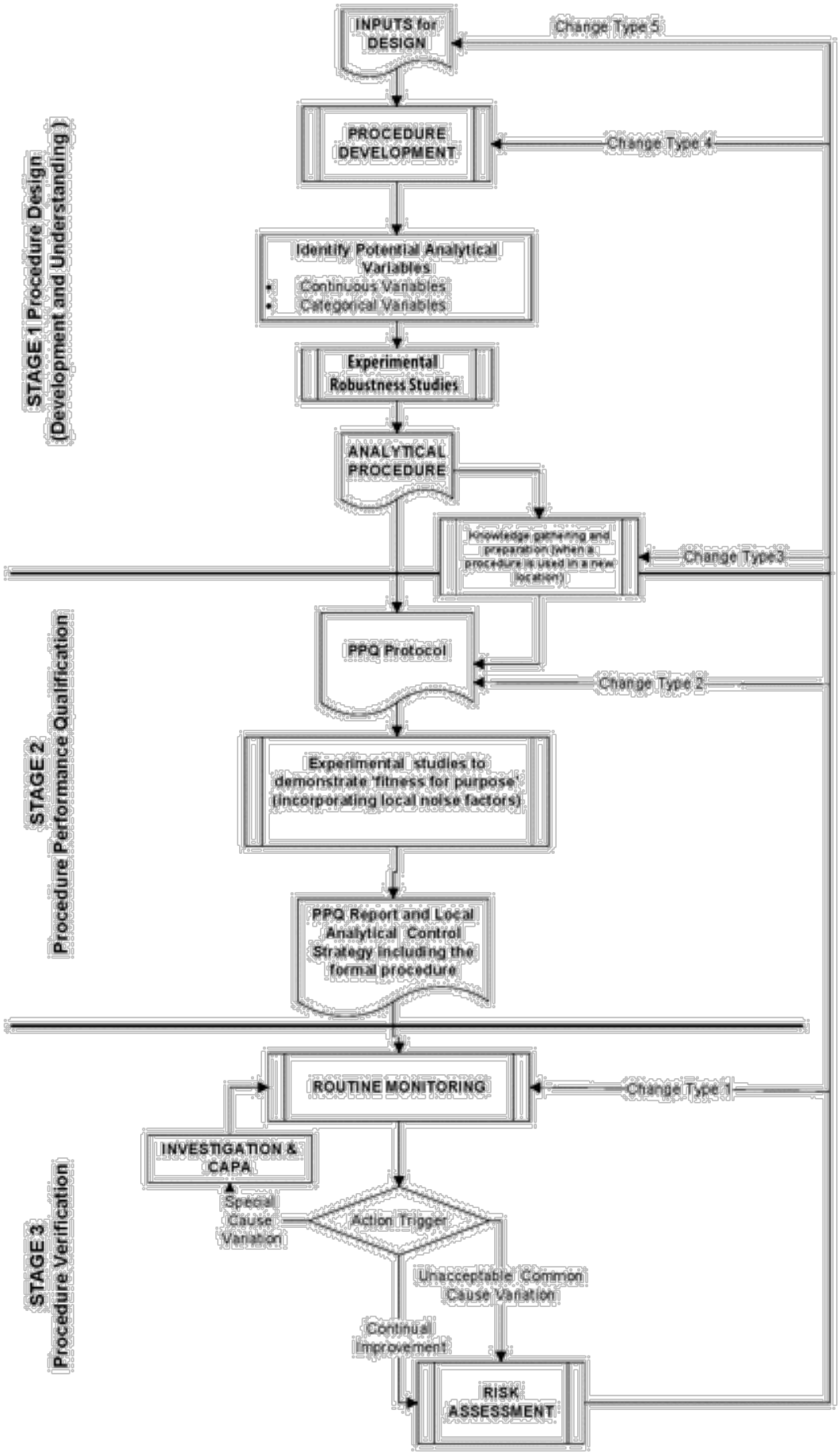

Figure 6. Three stages in the proposed lifecycle approach.

[NOTE——Refer to *Continual Improvement* (below) for a description of the different types of change.]

Risk-assessment tools (see ICH Q9 for examples) then can be used to identify potential procedural variables that may need to be controlled to ensure procedure performance and to prioritize experimentation to eliminate or mitigate areas of risk. CNX can help classify all the variables. As part of this exercise it is important to provide justifications (for example, prior knowledge or scientific rationale) for the assignments made.

Based on historical knowledge and an assessment of risk, analysts can make and document decisions about which variables will be classified as C and fixed and which variables will be classified as X and investigated experimentally. During the procedure-development phase, analysts identify certain variables that are fundamental to the procedure design, e.g., detector or column type. These are classed as control variables and are not further explored during the procedure-understanding phase of Stage 1.

Experimental Robustness Studies

Experimental robustness studies address the variations that may occur as the procedure is performed on different occasions. These studies consider both continuous and categorical X (eXperimental) variables. Continuous variables (e.g., temperature, pH, or flow rate) typically are studied via design of experiments (DoE). For these continuous variables, the output of the DoE study could be a procedure design space within which the procedure performance is ensured. For categorical variables (like column packing batch, type of instrument, etc.) the DoE study attempts to highlight variables that could have a significant effect on procedure performance regarding accuracy and precision, although these variables may have an even greater effect later in the life cycle. During this study, variables may be identified and may be considered too difficult or expensive to control. These are defined as Noise (N) variables in the CNX scheme. Although N variables are not directly studied at this stage, they are assessed indirectly as part of the Stage 2 activities when a laboratory has to confirm that the analytical control strategy is adequate to allow the procedure to produce reportable results that meet the requirements of the ATP in a particular environment. Example N variables include environmental and routine operating conditions.

As a result of the robustness study, a set of operational procedure controls with respect to the C and X variables are defined as part of the Analytical Control Strategy.

When uncontrolled categorical variables may result in unacceptable procedure performance, analysts should consider including a check or system suitability test (e.g., chromatographic resolution, symmetry factors, etc.). When such a check is included, it is good practice in the analytical procedure to explain the purpose of the check and the specific categorical variables it is designed to monitor.

Knowledge Gathering and Preparation

This step focuses on ensuring that any location where the procedure is intended to be operated is adequately prepared to use the procedure. It is the transition step between Stage 1 and Stage 2 where effective communication channels need to exist between the laboratories. The knowledge gathered to develop the procedural understanding should be shared as needed in support of the implementation of the control strategy across sites that intend to use the analytical procedure.

The extent of the knowledge required should take into account the level of preexisting knowledge of the analysts at the new location with respect to the product, analytical method, or procedure. The analytical procedure conditions and detailed operating controls, along with all of the knowledge and understanding generated during the design phase and any performance history should be conveyed to or summarized for staff at the location where the analytical procedure will be used.

STAGE 2—PROCEDURE PERFORMANCE QUALIFICATION

The objective of this stage is to demonstrate that the procedure is fit for purpose. This stage confirms the analytical procedure is capable of delivering reproducible data that consistently meet the performance criteria defined in the ATP while operated subject to the noise variables that may be experienced. Therefore, procedure performance qualification must be performed before routine application of the analytical procedure by the user laboratory.

Procedure performance qualification is carried out either to qualify a new procedure or to revise the conditions or operating environment of an established procedure.

Showing an analytical procedure is fit for purpose involves demonstrating that the defined analytical procedure will, under routine operating conditions, produce data that meet the target measurement uncertainty defined in the ATP. The procedure performance qualification experiments, e.g., precision studies, should be designed to challenge analytical performance characteristics that relate to the ATP requirements and should be based on sound science and risk as well as prior knowledge and understanding.

The analytical procedure used in the procedure performance qualification study should be based on available knowledge and understanding. The analytical control strategy will be refined and updated as a consequence of any learning from the study. For example, further controls may be added to eliminate sources of variability that are identified in the routine operating environment in an analytical laboratory, or replication levels (multiple preparations, multiple injections, etc.) may be increased to reduce the overall uncertainty in the reportable result (format of the reportable result).

When analysts believe there may be a residual risk of variation in the performance of the procedure, they may add appropriate checks to detect any unacceptable levels of variation in the performance of the procedure. These system suitability checks should focus on analytical performance characteristics that may be affected by noise and should be controlled to ensure the requirements of the ATP are consistently met. For example, if there is a residual risk of variation in separation performance due to the risk of batch-to-batch variation in column packing material and the degree of separation is known to have an effect on the uncertainty of the data, a check may be included to ensure that peak resolution is sufficient to meet the ATP requirements. Examples of system suitability tests for chromatographic systems are described in general chapter Chromatography <621>.

When end users do not have access to knowledge and understanding acquired during procedure development, e.g., for compendial procedures, users should recognize this additional risk and ensure the procedure performance qualification study and local or compendial analytical control strategy adequately mitigate associated risks. End users also must ensure that an appropriate control strategy for the procedure is applied.

STAGE 3—CONTINUED PROCEDURE PERFORMANCE VERIFICATION

The purpose of this stage is to provide ongoing assurance that the analytical procedure remains in a state of control throughout its lifecycle.

This stage includes both routine monitoring of the analytical procedure's performance and evaluation to determine if the analytical procedure, as a result of any change, is still fit for purpose.

A system or systems for detecting unplanned departures from the analytical control strategy is essential to accomplish this goal. Adherence to cGMP requirements, specifically, the collection and evaluation of information and data about the performance of the procedure, allows detection of undesired variability. Evaluating the performance of the procedure identifies problems and determines whether action must be taken to correct, anticipate, and prevent problems so that the procedure remains in a state of control.

Routine Monitoring

Trend analysis using methodologies such as control charting can be conducted on the main performance indicators to confirm that the analytical procedure remains in a state of control.
This stage should include an ongoing program to collect and analyze data that relate to analytical procedure performance, for example, from replication of samples or standards during the analysis or by trending system suitability data. This activity aligns with the guidance in *Analytical Data—Interpretation and Treatment* <1010> on system performance verification. Close attention should also be given to any out of specification or out of trend results generated by the analytical procedure once it is being operated in its routine environment.
If, during routine monitoring of the procedure, data indicate the procedure is out of control or there is an opportunity or need for improvement, then further action is taken.

There are three action triggers (see *Figure 6* for examples):

- special-cause variation (e.g., new, unexpected phenomenon)
- unacceptable common cause variation (e.g., expected variability inherent in the procedure)
- continual improvement.

Observed Variations

During the investigation, particular attention should be given to special cause variation (shifts, drift, and deviation) and common cause variation (unacceptable noise) (*Figure 7*). Variation may result when a particular procedure variable is not adequately controlled. This variation may arise for a number of reasons:

- A variable was not identified or adequately studied during the procedure understanding study (Stage 1), and therefore no proper control was defined.
- A variable was not identified or adequately studied during Stage 2 (precision study), and therefore no proper control was defined.
- Series member of a set of categorical variables (not included in the DoE, Stage 1) has been found to have an effect on performance (e.g., a new batch of column packing results in unacceptable performance).
- A control strategy was defined but not followed.
- A noise variable has been found to have an impact on routine performance.

Investigations into inadequate performance should be thorough and well documented and should aim to reach a conclusion about the variable that is truly the root cause. Corrective and preventive action should be taken to ensure the analytical control strategy is updated in the analytical procedure.

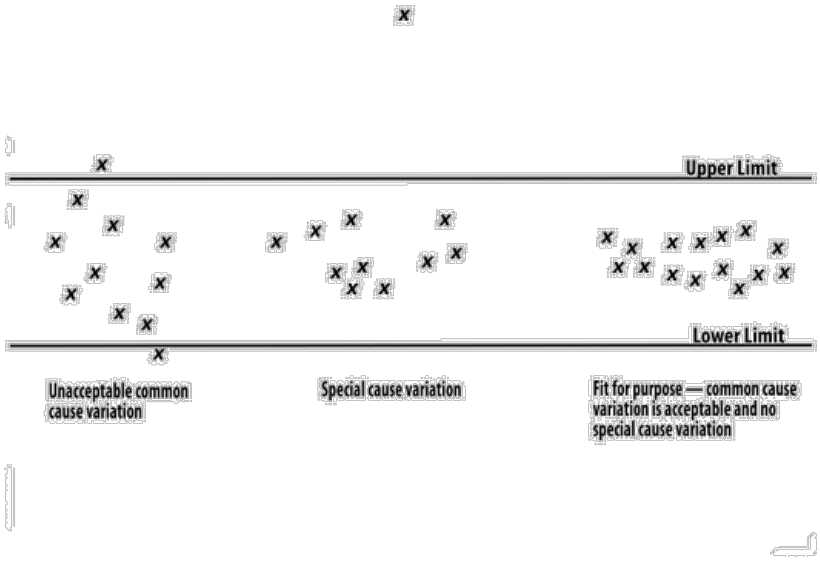

Figure 7. Common variation and special variation.

Continual Improvement

Throughout the procedure's lifecycle, changes may be required to improve the operational performance or the control strategy (continual improvement). Changes may include but are not limited to: inclusion of an additional control, introducing a new method or technology, changing the intended purpose to incorporate a new impurity or tighten specifications, or alignment with a procedure in a compendial monograph that has been updated. The nature of the change dictates the action that should be taken, and a risk assessment should be performed to identify what action is required, and the change should be documented. When the risk assessment identifies a change that requires qualification, the activities described in Stage 2 are performed. This stage also applies to modifications of compendial procedures.

EXAMPLES OF CHANGES AND APPROPRIATE ACTIONS

Change Type 1: Changes that are within already proven ranges (within the procedure's design space) are considered adjustments and do not require a procedure performance qualification study to be performed before returning to routine monitoring.

Change Type 2: These are changes that are outside the already proven ranges but require only confirmation that the procedure continues to generate data that meet ATP requirements. Full procedure redevelopment is not required.

Change Type 3: These are changes that involve the need to operate the analytical procedure in a different environment. These types of changes traditionally have been treated as a procedure-transfer exercise (or procedure verification when a pharmacopeial procedure is used for the first time in a new environment).

Change Type 4: This is a change that may require a new analytical procedure, but the ATP remains the same. The procedure will return to the procedure development stage.

Change Type 5: This change involves tightening a specification limit or a change to the intended purpose of the procedure to measure additional attributes. These changes result in a new ATP being defined.

CONCLUSION

The Expert Panel recommends adoption of a lifecycle approach for the management of analytical procedures. This approach builds on and enhances the current information contained in several *USP* general chapters and ICH guidance documents. Adoption of this approach would introduce new concepts to the *USP*: the Analytical Target Profile and associated predefined acceptance criteria, evaluation of the uncertainty associated with the analytical procedure, incorporation of risk analysis strategies, and consideration of the potential effect of changes to an analytical procedure in the context of the analytical procedure's lifecycle. *Table 1* shows the key advantages of adopting a lifecycle approach.

Table 1. Advantages of Adopting a Lifecycle Approach for Managing Analytical Procedures

Current Approach	Lifecycle Approach
Focus is showing that various procedure performance characteristics meet criteria—but may not consider how these relate to the overall uncertainty in the data and whether they are acceptable or not	The driver is understanding the target measurement uncertainty, which is the maximum level of measurement uncertainty that represents fitness for purpose (i.e., ensures decisions from data are made with a predefined confidence) and to demonstrate the procedure will meet this uncertainty requirement
Tendency to perform validation in a check box manner against the general analytical performance characteristics described in <1225> and ICH Q2	Specific ATP for each measurement requirement defining the characteristics and criteria that the procedure should meet
Limited understanding of effects of variation on performance	Structured and methodological approach to identify and explore variables

Current Approach	Lifecycle Approach
Validation, verification, and transfer are seen as separate exercises	All are integrated as part of the analytical procedure lifecycle, and success is demonstrated by generating reportable results that are consistent with the ATP
Confusion about the differences among procedure validation, procedure transfer, and procedure verification	Improved clarity and holistic view with the ATP as the focal point
Separate guidances in *USP* covering validation, verification, transfer of analytical procedures, and system performance verification	A single guidance for a lifecycle approach for analytical procedures

As a result of these recommendations, the Validation and Verification Expert Panel proposes that the concepts addressed in <1225>, <1226>, and <1224> be revised to integrate the processes for demonstrating that an analytical procedure is fit for purpose throughout its lifecycle and that these three chapters be compiled into a single general information chapter <1220> and a new general chapter <220> that specifies the basic requirements.

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