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Analytical Control Strategy

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ABSTRACT The concepts of quality risk management (QRM), analytical control strategy (ACS), and knowledge management (KM) were briefly introduced in a previous *Stimuli* article titled *Lifecycle Management of Analytical Procedures: Method Development, Procedure Performance Qualification, and Procedure Performance Verification*, published in *PF* 39(5). In this *Stimuli* article, the USP Validation and Verification Expert Panel provides a more in-depth discussion on how an ACS that has been developed, maintained, and updated using the QRM process described in ICH Q9 (*1*) can improve the decision-making methodology during the lifecycle of the analytical procedure. This article explains how the ACS needs to be maintained in order to stay current and ensure that the analytical procedure will deliver a reportable value that meets the analytical target profile (ATP) requirements continuously throughout the analytical procedure lifecycle. A comprehensive discussion is also provided on the development of the ACS, how it applies to sample preparation and measurement, and how a suitable replicate strategy can be developed to ensure that the ATP is met. The Expert Panel would appreciate any feedback on the suggested approach, as well as any alternative approaches for consideration.

In this article, the following questions are considered:

- What is the ACS?
- What is the relationship between the ACS and the ATP?
- What is the QRM process and how can it be applied to an analytical procedure?
- How does the ACS apply to the product lifecycle?

Examples of the following are provided:

- How to develop an ACS using the QRM process
- How to develop and apply a risk-based replicate strategy to minimize variability (*Appendix*)

This article is intended to be a companion to a separate *Stimuli* article discussing the ATP, appearing in the same issue of *PF*.

INTRODUCTION

Fundamental to the concept of quality by design (QbD) is to start with the end in mind. When a QbD approach is applied to a pharmaceutical manufacturing process, the initial step is to develop a quality target product profile, which defines the design criteria for the product and forms the basis for the development of the product critical quality attributes (CQA) and control strategy. The same QbD concepts can be applied to the design and development of analytical procedures by considering the reportable value as the product of an

analytical procedure. In this case, an analytical target profile (ATP) is prepared, which forms the basis for development of the analytical control strategy (ACS).

To ensure that the requirements defined in the ATP (*2*) are met, one must identify those analytical procedure variables that have the potential to impact the reportable value (accuracy and precision). It is important to understand how variations in these variables impact the results and to define controls that ensure the target criteria are met.

WHAT IS THE ANALYTICAL CONTROL STRATEGY?

In alignment with ICH Q10 (*3*), the ACS is a planned set of controls, derived from an understanding of the requirements for fitness for purpose of the reportable value, an understanding of the analytical procedure as a process, and the management of risk, all of which ensure the performance of the procedure and the quality of the reportable value, in alignment with the ATP, on an ongoing basis. Once it has been derived from management of risk, the ACS should lead to assurance of consistent quality of the output of the analytical procedure in alignment with the ATP. Theoretically, each and every step in the analytical procedure, from sampling to the final reportable value, can potentially be a contributor to the measurement uncertainty of the reportable value.

The evaluation of the risk posed by each variable and how it may impact the reportable value should be based on scientific knowledge, prior experience, and experimentation. Using quality risk management (QRM) proactively will lead to an understanding of the linkage between procedure variables and the accuracy and precision of the reportable value as well as interdependencies of the different variables. Strategies for the analytical procedure controls can be designed to reduce input variation, adjust for input variation to reduce its impact on the output, or combine both approaches. This systematic approach should ensure that the performance of the analytical procedure can be explained logically and/or scientifically as a function of procedure parameters/inputs, and is most effective when supported by good knowledge sources. The sources of knowledge can include: prior knowledge (public domain or internally documented); expertise (education and experience) or experience with similar applications; and product-/process-specific knowledge developed and/or acquired with each application as it becomes available. QRM and knowledge management (KM) are enablers and support the ACS throughout the analytical procedure lifecycle, from development through qualification and routine commercial use. The linkages between ACS, QRM, and KM are illustrated below in *Figure 1* (*4,5*).

Figure 1. Linkages between the ACS, QRM, and KM.

Analytical Unit Operations

Development of the ACS requires consideration of all aspects of an analytical procedure that might impact the reportable value. A unit operation is any part of a potentially multiple-step process that can be considered to have a single function with clearly defined boundaries. For an analytical procedure, three distinct unit operations can be identified, as shown in *Figure 2*. The unit operations for an analytical procedure are illustrated and described below.

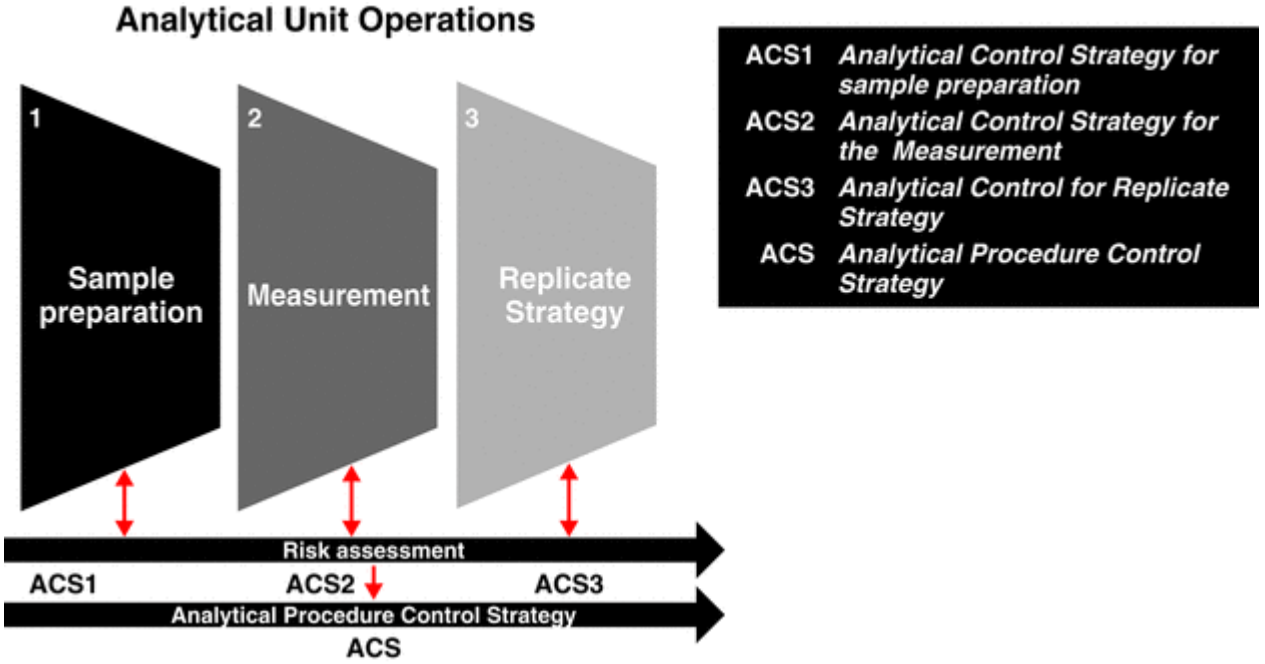


Figure 2. Three distinct unit operations of the analytical procedure.

TEST SAMPLE PREPARATION

The objective of the sample preparation unit of operation is to convert the laboratory sample into a test preparation suitable for measurement. This analytical unit operation includes all steps starting from sampling the batch to provide a representative laboratory sample for the testing lab; to laboratory handling, sub-sampling, splitting, and sample preparation procedures such as weighing, extraction, and dilutions; to the final analytical test preparation or solution. Although the sampling and representativeness of the laboratory sample are essential elements, and their potential impact on measurement uncertainty cannot be ignored, these will not be discussed in this article (*6*).

The sample preparation step needs to ensure that the analyte does not undergo any significant changes in its properties from the moment of sampling to the time when the actual analysis is carried out. These changes can be chemical, microbial, enzymatic, or physical. Depending on the technique used, this step can take a large variety of forms. It can be as simple as dissolving a known amount of drug substance in a known volume of solvent, or as complicated as complex extractions or derivatization. In all cases, the objective of this step is to maintain the integrity of the analyte in the sample (*7*). For example, where the test sample is a solution, there are two aspects that need to be considered: completeness of the dissolution/extraction and stability of the analyte from the time of preparation until the measurement. For an infrared identification test, the preparation of the pellet should not induce form changes; for a dissolution test, it is important to maintain the amount dissolved from the time of sampling from the dissolution vessel to the measurement [high-performance liquid chromatography (HPLC) or ultraviolet].

MEASUREMENT

This is the step where a relationship between the analyte in the test sample and a signal that can be detected or measured is established. This relationship can be qualitative (e.g., identification tests), or quantitative, where a mathematical relationship between the concentration of the analyte in the test solution or test sample and the measurable signal can be established. The analysis can be instrumental or classical (wet chemistry) and can employ a large variety of techniques. Classical quantitative analysis is achieved by measurement of weight or volume, while instrumental procedures use a detector to measure physical or chemical quantities of the analyte such as light absorption, fluorescence, or conductivity.

For this step, it is important to ensure that the signal measured or observed is specific to the analyte, and the signal response and concentration are defined by a known relationship over the concentration range of interest.

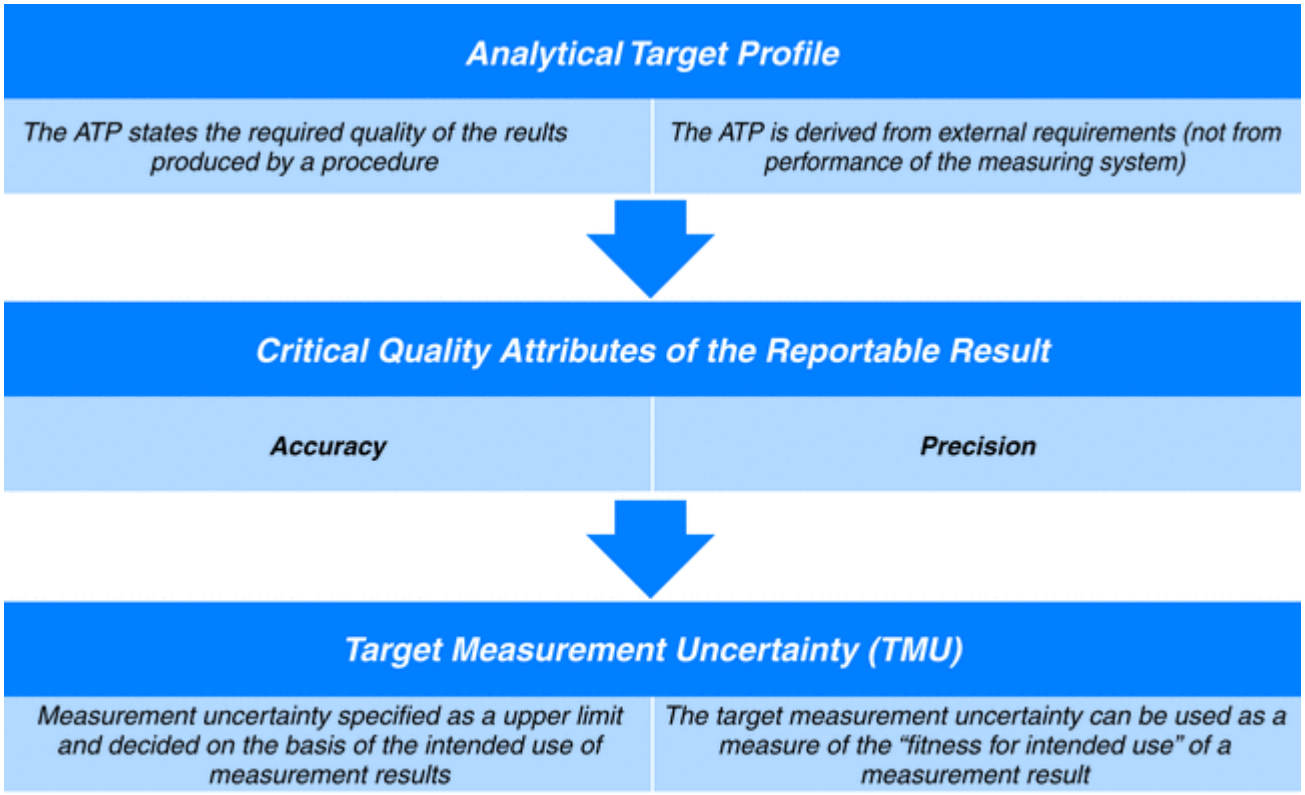
REPLICATE STRATEGY

USP General Notices, 7.10. Interpretation of Requirements, states, "The reportable value, which often is a summary value for several individual determinations, is compared with the acceptance criteria. The reportable value is the end result of a completed measurement procedure, as documented." Depending on the analysis unit operation, these individual determinations—or "format of the reportable value" (see *Biological Assay Validation* ⟨1033⟩)—may include several replicate levels, such as injections and sample preparations in liquid chromatography, or applications of the same test solution, several test solutions, and several titer plates (independent series) in the case of bioassays. The impact of increasing the replicates on the precision of the reportable value depends on the corresponding variance contribution, because increasing the number of injections will have no impact on the variance of the sample preparation, for example. Therefore, it is the objective of precision studies to achieve a reliable estimate of the variance contributions of an analytical procedure as the basis of a scientifically sound definition of the replicate level (see *Appendix*).

Because the unit operations are sequential, and some of the process steps are linked by input-output relationships, it is important to consider controls for unit operations that have an impact on downstream processing and/or end-product quality. For example, the output of the sample preparation unit of operation is input in the measurement unit. Therefore, aspects and attributes of the test sample preparation may affect the measurement. For example, for an HPLC procedure, a suitable control strategy has been developed and optimized to ensure stability and extraction of the analyte. However, if the sample solvent is not compatible with the mobile phase, or the concentration of the analyte in the test sample does not afford adequate detection or is out of the detector's linear range, this will introduce bias or increase variability, and ultimately the accuracy and precision of the reportable value will be compromised and the requirements of the ATP will not be met. It should be noted that some of these variables tend to be applicable on a general basis, and controls for these have already been implemented. Examples of variability can originate from weighing, pipetting, volumetric flasks, HPLC flow rate, or injection volume, just to name a few. These are controlled by the instrument/equipment qualification/calibration programs that are an integral part of a firm's good manufacturing practices. Other variables are specific to the product, technique, and/or analytical procedure.

What is the relationship between the ATP and ACS?

The relationship between the ATP, CQA of the reportable value, and the target measurement uncertainty (TMU) are illustrated in *Figure 3* below.



International Vocabulary of Metrology the International Vocabulary of Metrology–VIM editi VIM edition 3 Guide JCGM 200:2008 [ISO/IEC Guide 99:2007]
www.bipm.org/en/publications/guides/vim.html

Figure 3. Relationship between the ATP, CQA, and TMU.

The ATP considers the acceptable level of risk of making an incorrect decision with the reportable values. Setting decision rules (*8*) may assist in this area but they are not always necessary. As a first consideration, the acceptable level of risk should be linked to patient safety and efficacy and the risk of erroneously accepting a batch that does not meet specifications. Manufacturer risk—i.e., the risk of erroneously rejecting a lot that meets specifications [a false out-of-specification (OOS) result]—can also be considered when criteria for risk are established. Accuracy and precision are CQAs and are described by the measurement uncertainty and bias associated with the reportable value generated by the analytical procedure. The TMU is the maximum acceptable uncertainty for the reportable value in order to meet the ATP and therefore accomplish the fitness-for-purpose requisite for the analytical procedure. The TMU (if stated in the ATP) can be used as a target for development criteria for the analytical procedure qualification and standard for monitoring the performance of the analytical procedure during routine use. The role of the ACS is to ensure that the TMU is met on a consistent basis over the entire lifecycle of the analytical procedure, and therefore the reportable value conforms to the ATP.

A detailed discussion on accuracy, bias, total error, and TMU is provided in the *Analytical Target Profile: Structure and Application throughout the Analytical Lifecycle Stimuli* article intended to be a companion to this article.

It is not the intent of this paper to discuss the theory and provide guidance on calculation of measurement uncertainty and TMU. Detailed guidance on these concepts is available (*9*–*11*).

What is the QRM process and how can it be applied to an analytical procedure?

The path to an effective ACS is the QRM process. The QRM for an analytical procedure is a systematic process for the assessment, control, communication, and review of risk to the quality of the reportable value across the analytical procedure lifecycle (see *Figure 4*). Although ICH Q9 (*1*) refers to the risk to the quality of the pharmaceutical product, and ultimately the impact on the patient, in the context of the analytical procedures the risk refers the quality of the reportable value, which is the product of the analytical procedure.

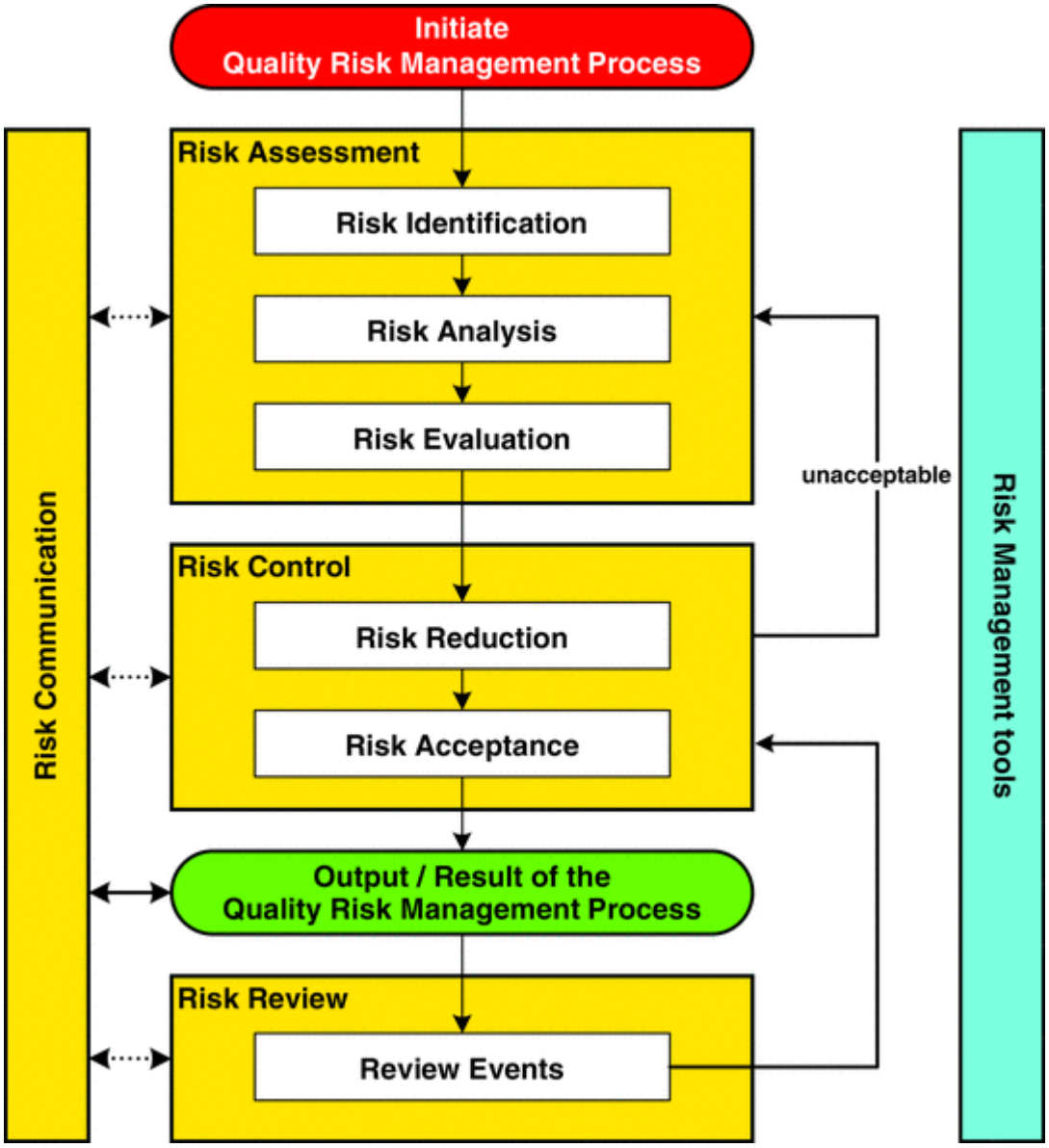


Figure 4. Overview of a typical QRM process (ICH Q9).

The ACS is the totality of steps taken to eliminate the risk or control it at an acceptable level. The risk is a combination of severity, probability, and detectability. The severity rating relates to the actual impact on the CQA, and it will not change as result of the QRM process. However, reducing the probability of occurrence and increasing the detectability are steps that will reduce the risk to an acceptable level.

Risk Assessment

This is the stage of learning and developing understanding about which analytical variables, such as material attributes and analytical procedure parameters, affect the quality attributes of the reportable value and how they have these effects. Based on scientific principles, experience, and prior knowledge, the following types of variables may be considered for analytical procedures: 1) variables related to materials (e.g., reagents, solvents, or reference standards); 2) procedure variables (e.g., equipment/instrument settings); and 3) environmental variables (e.g., light, moisture, or temperature). Not all variables need to be studied. At this stage, decisions can be made as to which of these variables can be controlled and which ones do not represent risk (therefore, they will not be subject to further consideration). By completing the risk assessment step, one will be able to answer the following questions: What might go wrong? What is the likelihood (probability) it will go wrong? What are the consequences (severity)?

1. Risk identification is the first step in the risk assessment process. It requires a systematic use of information to identify hazards referring to the risk question or problem description. Risk identification addresses the question, What might go wrong?
2. Risk analysis is the estimation of the risk associated with the identified hazards. It is the qualitative or quantitative process of linking the likelihood of occurrence and severity of harms. In some risk management tools, the ability to detect the harm (detectability) also factors into the estimation of risk. Risk analysis addresses the question, What is the likelihood (probability) it will go wrong?
3. Risk evaluation compares the identified and analyzed risk against given risk criteria. Risk evaluation considers the strength of evidence for all three of the fundamental questions. Risk evaluation addresses the question, What are the consequences (severity)?

Risk Control

Risk control includes decision making to reduce and/or accept risks. The purpose of risk control is to reduce the risk to an acceptable level. The amount of effort used for risk control should be proportional to the significance of the risk. Risk control might focus on the following questions: Is the risk above an acceptable level? What can be done to reduce or eliminate risks?

1. Risk reduction focuses on processes for mitigation or avoidance of risk to quality when it exceeds a specified (acceptable) level. The risk assessment step provides the knowledge and understanding as to which of the variables studied impact the accuracy and precision of the reportable value and will ultimately result in increasing the measurement uncertainty to an unacceptable level (i.e., exceeding the TMU). These will then be the variables that will be subject to controls developed at this stage. It is also important to note that this process is iterative; if some of the critical variables cannot be controlled adequately, the analytical procedure development/design stage may need to be revisited and adequate changes implemented. Once a preliminary ACS is developed, it is recommended to carry out a verification step to ensure that all critical variables have been studied and the sources of variability and bias have been eliminated or reduced to an acceptable level so the analytical procedure will generate a reportable value that meets the ATP.
2. Risk acceptance is a decision to accept risk. Risk acceptance can be a formal decision to accept the residual risk or it can be a passive decision in which residual risks are not specified. Risk cannot be completely eliminated. The objective of the ACS is to reduce and maintain the risk at an acceptable level. An analytical procedure may be used over a long period of time, and it can be expected that materials, equipment, or other factors may change. An example that most analytical chemists are familiar with is the column-to-column variability. Although incorporating column age as a variable in the risk assessment process is reasonably feasible, the performance of the column over a number of years cannot be predicted or assumed. The risk associated with using a different batch of packing material cannot be controlled, but the risk can be reduced by including a system suitability check, such as

resolution, as a mechanism for detecting unacceptable variation. There may be other potential sources of residual risk such as changes in reagents or equipment.

There are several examples of publications on risk assessment and applications of QRM methodology to analytical procedures (*12–14*).

Risk Communication

Risk communication is the sharing of information about risk and risk management between the decision makers and others. Any learnings gained during the QRM process as described above should be documented in order to communicate shared knowledge. KM is an important component of risk communication.

Risk Review

Risk review should be an ongoing part of the quality management process. The performance of the procedure should be reviewed on a regular basis. This is part of the routine monitoring process and is discussed later in this document.

QRM Methodologies

Risk assessment tools are used to support science-based decisions. It should be noted that no single tool is appropriate for all cases, and specific risks do not always require the same tool. A great variety of tools is listed below, but other existing or new ones might also be used. It is recognized that different companies, consultancies, and competent authorities may promote the use of different tools based on their culture and experiences; some of these are listed below. It is important to select the most appropriate tool for a given process, with the understanding that the level of formality and extent of documentation will be dictated by the risk in question. Results of the risk assessment can be presented either qualitatively or quantitatively. Some examples of risk management methodologies are provided below.

Basic risk management facilitation methods include flowchart, check sheets, process mapping, cause and effect diagrams (Ishikawa/fishbone).

Better-known risk evaluation and analysis methods include failure mode effects analysis (FMEA), failure mode effects and criticality analysis (FMECA), fault tree analysis (FTA), hazard analysis and critical control points (HACCP), hazard operability analysis (HAZOP), and risk ranking and filtering. It is not within the scope of this article to detail these, but excellent sources of information are available in several publications. An outstanding summary on the tools and how they are applied is provided in "Quality Risk Management ICH Q9; Annex I: Methods & Tools" (*15*).

Design of Experiments

Design of experiments (DoE) is a fundamental methodology for the QRM process. It is a systematic method to determine the relationship between potential variables of an analytical procedure and their impact on the output (i.e., the reportable value). In other words, it is used to find cause-and-effect relationships. In a properly constructed DoE, variables that could potentially impact a procedure will be identified and varied simultaneously in a carefully planned manner such that their individual and combined effects on the output can be identified. Fractional factorial designed experiments can be used to efficiently screen variables to determine which have the greatest impact on the output, whereas full factorial designed experiments will help to reveal significant interactions among the variables. This methodology allows

for a significant reduction in the number of experiments needed, compared with the classical one-variable-at-a time approach where the rest of the variables are held constant. Furthermore, DoE is more robust and feasible for a complicated process. DoE also utilizes statistical data treatment, which allows clear determinations regarding the significance of a variable and/or its interactions with regard to the output.

DEVELOPMENT OF AN ACS USING THE QRM PROCESS: STAGE 1

In this article, an example is provided in which a few variables were selected to illustrate how the principles of QRM can be applied. Using these principles, a comprehensive ACS can be developed by considering possible variables and systematically applying the QRM approach to each of these. The example uses a simplified scenario and significantly fewer variables than is typical in real cases. The development of an ACS can be more complex when the number of variables is significantly greater than in this example. However, the example is useful in providing a "walk through" of the process, including the steps involved, the scientific considerations, and the use of risk management tools.

The QRM process begins once an appropriate analytical technique has been selected and tentative procedure conditions have been chosen. At this time, as a result of the preliminary screening, major sources of bias may also be identified and reduced or eliminated by the choices of technology and procedure conditions. The aim of the QRM process is to take the proposed procedure conditions and identify appropriate controls on the process inputs that will ensure the desired process output (i.e., a reportable value that meets the requirements stipulated in the ATP).

The first step in the QRM process is the risk assessment, which starts with the risk (hazard) identification. At this time, the question is, What might go wrong? The risk identification step begins by developing a process flow chart highlighting the key steps involved in the analytical procedure. For an HPLC procedure, an example of a process flow chart is shown in *Figure 5*.

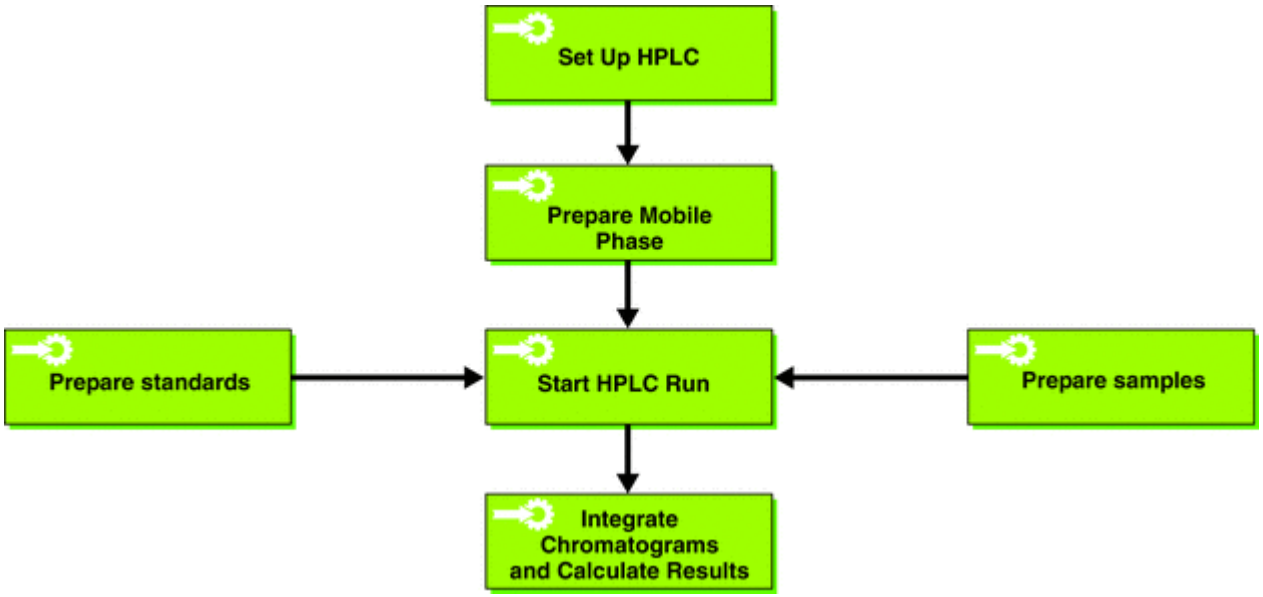


Figure 5. An example of a process flow chart for an HPLC procedure.

Each high-level step in the process can be further broken down using process mapping tools. For example, the sample preparation step can be broken down into a number of detailed sub-steps, as shown in *Figure 6*.

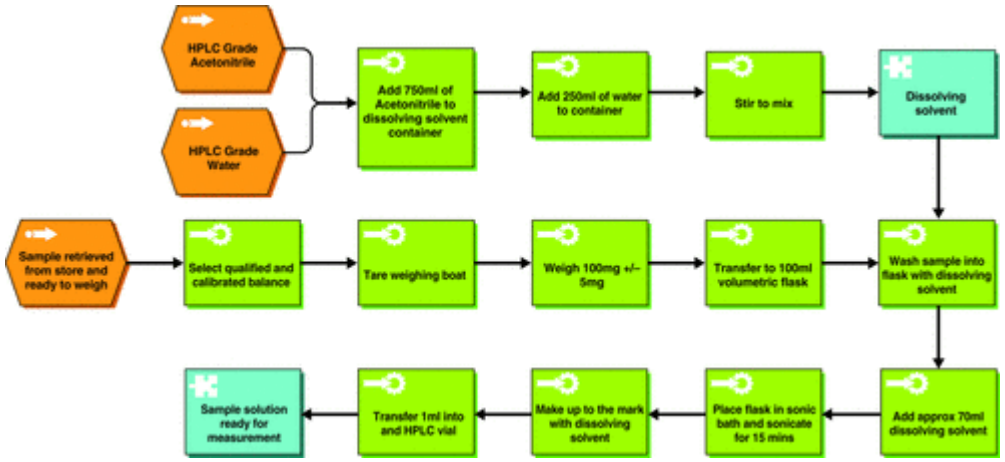


Figure 6. The sample preparation step, broken down into detailed substeps.

This detailed process map can then be used to identify the variables associated with the process. Ishikawa diagrams (fishbone diagrams) can be used in conjunction with the detailed process maps to identify the potential variables. In the example below (*Figure 7*), a range of potential variables associated with the use of the sample preparation step is illustrated.

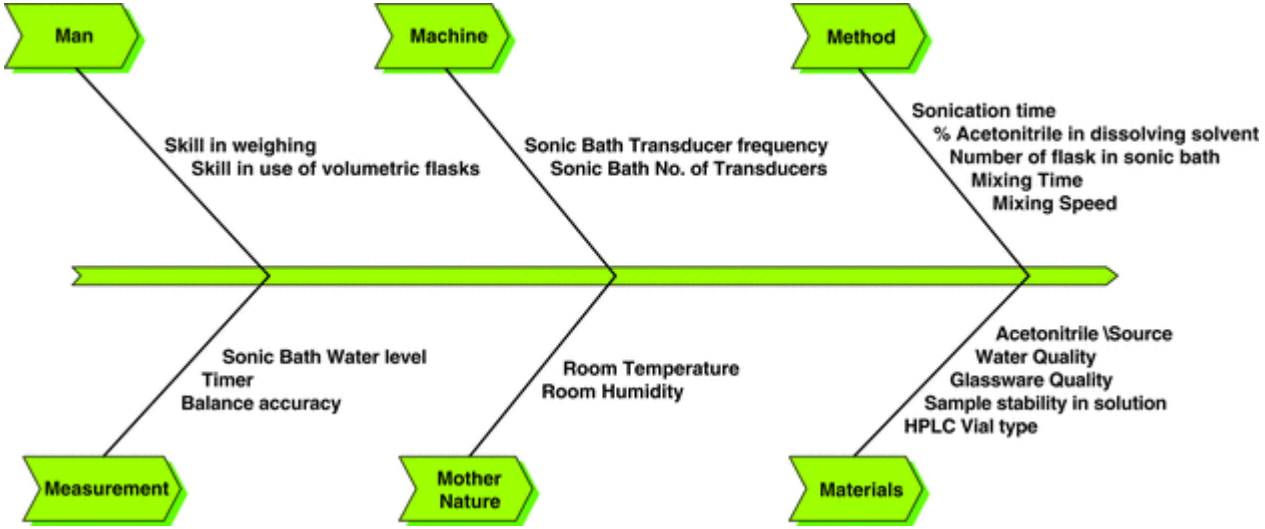


Figure 7. Ishikawa (fishbone) diagram, used to identify potential variables.

Note that the Ishikawa diagram is used in helping to brainstorm potential variables and, as with any type of brainstorming, no judgment should be made at this stage on whether a variable is likely to be critical or not. The aim is simply to ensure that the list of variables is as comprehensive as possible.

Risk Assessment

1. RISK IDENTIFICATION

The first step in the assessment is risk identification. It answers the question, What can go wrong?

To illustrate this and the subsequent steps in the QRM process, we will focus on a small selection of variables associated with the sample preparation and HPLC setup steps in the process flow diagram. This is a subset of the total list of variables that may need to be examined.

Variables for sample preparation unit of operation:

- % Acetonitrile in the sample solvent
- Sonication time
- Analyst skill in sample preparation
- Humidity of the laboratory
- Quality of acetonitrile used in the dissolving solvent
- Variables for the measurement unit of operation (HPLC setup):
- Column temperature
- % Acetonitrile in the mobile phase
- Batch of packing material used in the HPLC column
- Quality of the acetonitrile

For most samples, the relative organic/aqueous composition of the mobile phase is likely to be important in ensuring complete dissolution of the sample, which if not achieved would lead to an inaccurate result. Also, where the solution composition is critical to dissolution, there is an increased likelihood that minor variation in the preparation of the dissolving solvent could lead to accuracy and/or precision issues when different batches of sample solvent are prepared. Similarly, sonication time may be important if the sample does not dissolve easily. The humidity of the laboratory may be important if the sample is impacted by humidity (e.g., it degrades or absorbs moisture). Analyst skill is important, as mistakes in sample preparation can impact both accuracy and precision.

The column temperature may affect retention time, resolution, and peak shape, potentially affecting resolution (accuracy). Effects on peak shape can potentially lead to inconsistent integration (precision). The percent acetonitrile in the mobile phase may impact the accuracy as it may be critical to achieving resolution of interfering peaks and may also impact precision by affecting the peak shape. The batch of packing material can be important to the quality of the separation and hence the accuracy of the results.

2. RISK ANALYSIS

The next step in the assessment is the risk analysis. The risk analysis answers the question, What is the likelihood (probability) it will go wrong?

Once all the potential hazards have been listed, the risk identification step is complete and the process then moves to the risk analysis step. At this step we are trying to estimate the risk associated with each of the variables. When considering the variables identified in the risk identification step, it will be possible to identify certain variables which, from prior knowledge, will be important to control within a

certain range (controlled variables). Some of these variables will be difficult or impractical to control or are known to be of low risk (noise variables), whereas some will require the performance of experiments to understand how critical they are and to determine the range over which they need to be controlled. The risk analysis process aims to identify, from the many variables in the output from the risk identification step, those for which an understanding of their impact on the reportable value is required in order to establish appropriate control limits.

A "heat map" can be a valuable tool to support a preliminary qualitative assessment of risks. The heat map provides a visual indication of which variables are considered to have a potentially strong impact (red), medium impact (amber), or minor impact (green) on the procedure performance in terms of accuracy and precision that can be related to the requirements of the ATP. Heat maps are dependent on previous knowledge and expertise of the chemist and the intended purpose of the analytical procedure. Readers may disagree with the assignment of the colors in the example but should consider this representative of the author's procedure, and may adapt the theory illustrated here to suit their own scenario. Based on the nine variables above, the heat map in *Table 1* was created.

Table 1. Example of a Heat Map

Analytical Unit of Operation	Variable	Potential Hazard	Accuracy	Precision
	% Acetonitrile in the sample dissolution solvent	Completeness of the Dissolution of the sample		
Sample preparation	Sonication time	Completeness of the Dissolution of the sample		
Sample preparation	Analyst skill	Incorrect sample preparation Weighing, dilutions, use of volumetric flask		
Sample preparation	Humidity of the laboratory	Moisture absorption can lead to inaccurate weighing or degradation		
Sample preparation	Grade of acetonitrile used in the dissolving solvent	Potentially can impact if contaminants interfere with the analyte		
Measurement (HPLC SetUp)	Column temperature	Column performance, resolution, peak shape		
Measurement HPLC SetUp	% Acetonitrile in the mobile phase	Column performance, resolution, peak shape		
Measurement (HPLC SetUp)	Batch of packing material used in the HPLC Column	Column performance, resolution, peak shape		
Measurement (HPLC SetUp)	Quality of acetonitrile	Potential impact can affect the baseline, and/or provide high background noise depending on the analytical wavelength		

The rationale for the risk level assignments is as follows. At this stage it is useful to separate the variables into those that can be controlled, those that cannot be controlled, and those that will be subject to further experimentation. An uncontrollable variable is one that may have an impact on the accuracy or precision of the data, but it is not possible to directly measure the relationship between the variable and the response in an experiment. In our example, it is not possible to understand and control how potential variability of column packing of future batches might impact the chromatography. Although these variables are not directly controllable and therefore not included in a DoE, they are still potential hazards that need to be considered in the ACS (see the example ACS below for how this risk might be mitigated).

The quality of acetonitrile used can be important for ensuring that no contamination is observed in the chromatography. An adequate control of the quality of the acetonitrile can be implemented by specifying the grade (HPLC) or HPLC and low-UV cut off, depending on the analytical wavelength, so further assessment of this variable will not be carried out.

Analyst skill is controlled by the good manufacturing practice (GMP) requirement in the form of mandatory training and demonstration of competence. Therefore, this variable is considered low risk. (Analyst-to-analyst or laboratory-to-laboratory performance of the analytical procedure will be evaluated as part of the intermediate precision study).

Humidity for both the sample preparation (the material is not hygroscopic or moisture sensitive) and the HPLC measurement step was assessed as low risk for this application, thus there was no need for it to be studied further.

Batch-to-batch variability of the column packing cannot be studied. Adequate performance of the column will be verified by the system suitability requirements to ensure performance of the analytical procedure. This risk has been mitigated by increasing detectability of the variation. The column-to-column variability, however, needs to be accepted as residual risk (see *Risk Acceptance* below).

This leaves four controllable variables that are considered to present potential risk. They are then studied in a DoE to determine the sensitivity of the variables, eliminate bias, and determine ranges where the quality requirement of the reportable value established in the ATP will be met. (When a significant number of variables requires an experimental study to understand their impact, a "screening DoE" may be performed first, to identify those with the greatest impact on the quality of the reportable value). The four selected variables and ranges for study are presented in the table below. The mid level is presented as the proposed condition of the analytical procedure. At this time, the range (high to low) needs to be expanded beyond values expected as normal fluctuations typically encountered during routine use. This is done to afford understanding and indisputably identify relationships if they exist between the variation and impact on the CQA of the reportable value. DoE experiments can easily be run using software to analyze a series of samples under the conditions stated in *Table 2*.

Table 2. Conditions for the DoE Experiment

Variable	High Level	Mid Level	Low Level
% Acetonitrile in sample solvent	80	65	50
Sonication time (min)	20	12	5
Column temperature (°)	45	35	(ambient; 25)
% Acetonitrile in mobile phase	80	70	60

The information from a DoE study indicated that all four of these variables (% acetonitrile in the sample solvent, sonication time, column temperature, and % acetonitrile in the mobile phase) have a strong correlation with the accuracy and/or precision of the data (i.e., the "severity of harm" from these variables is high). The risk assessment needs to consider not only the severity of harm (or strength of the relationship between the input variable and the desired output) but also the likelihood of occurrence—i.e., what is the probability that this variable will vary to the extent that quality of the reportable value will be impacted? The assessment of the severity can be combined with the assessment of probability of variation to give an overall risk score, and the resulting risk score can be further reduced by incorporating analytical procedure performance checks in the system suitability (as described earlier in *Risk Control*).

Risk Evaluation

Risk evaluation compares the risk versus the given risk criteria. The risk acceptance criteria (or the risk protection threshold) for this step is the TMU. Therefore, a risk target of 10 will correspond to the TMU. Any variable or combination of variables that equal or exceed the risk target of 10 will need to be controlled in ranges that will ensure the required performance of the procedure. If the above example is evaluated against the criteria, it would be concluded that all four of the variables exceed TMU and therefore should be subject to ACS (*Table 3*).

Table 3. Example of Risk Evaluation

Variable	Severity (from DoE) (1 low, 5 high)	Probability of variation (1 low, 5 high)	Risk score
% Acetonitrile in sample solvent	4	3	12
Sonication time (min)	4	3	12
% Acetonitrile in mobile phase	5	4	12
Column temperature (°)	5	2	10

Risk Control

RISK REDUCTION

Risk reduction can include actions to reduce the risk, reduce the probability, or improve the detectability. The DoE essentially can establish a quantitative relationship between the variable studied and the response (i.e., the TMU). Therefore, the DoE can also be used to predict ranges for the variables studied where the TMU will be met. The DoE results suggest that, in the ranges specified in *Table 4* below, the criteria will be met.

Table 4. Conditions for the DoE Experiment

Variable	High Level	Mid Level	Low Level
% Acetonitrilein sample solvent	70	65	60
Sonication time (min)	15	12	10
Column temperature (°)	40	35	30
% Acetonitrile in mobile phase	75	70	65

At this time, a verification step confirms that the ranges predicted are acceptable for three of the four variables studied. The % acetonitrile in the mobile phase, while it meets the risk threshold, is still marginal. As previously stated, because these variables affect the CQA, the severity component of the risk does not change; the risk can be reduced to an acceptable level by decreasing the probability of variation and increasing the detectability needed to reduce the risk (see *Table 5*).

Table 5. Example of Risk Evaluation

Variable	Severity (from DoE) (1 low, 5 high)	Probability of variation (1 low, 5 high)	Risk score
% Acetonitrile in sample solvent	4	1	4
Sonication time (min)	4	1	4
% Acetonitrile in mobile phase	5	2	10
Column temperature (°)	5	1	5

Adding a system suitability requirement to detect the hazard, before the harm occurs to the reportable value, reduced the risk from 10 to 2.5, which is well below the risk acceptance threshold (see *Table 6* and *Table 7*).

Table 6. Risk Assesment

Variable	Severity (from DoE) (1 low, 5 high)	Probability of variation (1 low, 5 high)	Detection	Risk Score (SxP)/D*
% Acetonitrile in mobile phase	5	2	4	2.5

*S: Severity; P: Probability; D: Detectability

Table 7. Risk Assessment After Implementation of the ACS

Analytical Unit of Operation	Variable	Potential Hazard	Control Strategy	Accuracy	Precision
Sample preparation	% Acetonitrile in the sample dissolution solvent	Completeness of the dissolution of the sample	Specify% acetonitrile in the sample solvent 65% +/– 5%		

Sample preparation	Sonication time	Completeness of the dissolution of the sample	Sonication time between 10 and 15min		
Sample preparation	Analyst skill	Incorrect sample preparation: weighing, dilutions, use of volumetric flask	Controlled by training mandated by GMP		
Sample preparation	Humidity of the laboratory	Moisture absorption can lead to inaccurate weighing or degradation	No impact		
Sample preparation	Quality of acetonitrile used in the dissolving solvent	Potentially can impact if contaminants interfere with the analyte	Specify grade of acetonitrile		
Measurement (HPLC Set Up)	Column temperature	Column performance, resolution, peak shape	Specify column temperature, 30 +/– 5°		
Measurement (HPLC Set Up)	% Acetonitrile in mobile phase	Column performance, resolution, peak shape	Specify % acetonitrile in the mobile phase 70% +/– 5%. Add system suitability requirement		
Measurement (HPLC Set Up)	Batch of packing material used in the HPLC column	Column performance, resolution, peak shape	Add system suitability requirement		
Measurement (HPLC Set Up)	Quality of acetonitrile	Potential impact can affect the baseline, and/or provide high background noise depending on the analytical wavelength	Specify grade of acetonitrile		

RISK ACCEPTANCE

Risk cannot be completely eliminated but it can be reduced to an acceptable level. As discussed earlier, the variability of the column packing for future columns cannot be controlled; and while the risk is reduced to an acceptable level, it cannot be eliminated completely.

The composition of the sample solvent was established and verified using drug substance samples available to the laboratory at the time of the analytical development qualification, and it is not likely to change during the product lifecycle. Therefore, the probability that the polymorph will vary from one lot to the next is negligible because the polymorph control is typically part of the drug substance specifications. However, because different polymorphs may have very different solubilities, in the case of a compendial procedure the suitability of the sample solvent should be verified as part of the procedure installation.

Although it is recognized that these types of studies are not new and an analytical chemist charged with developing an analytical procedure knows that important parameters need to be studied and optimized, historically these parameters have been evaluated in isolation, with no or little ability to fully understand the interactions between them. The USP Expert Panel believes that providing target acceptance criteria, linked holistically to the quality of the output, will trigger a systematic science- and risk-based strategy for development, qualification, and performance monitoring during routine use. This will improve overall performance of the analytical procedures by placing focus on the output. The output is held to the standard established in the ATP and directly linked to the fitness for purpose of the analytical procedure.

Today, computer-simulated experiments have prompted the development of new types of experimental designs and methods of analysis. These not only facilitate rational experimental designs, but also are able to assess a large number of variables with minimal experimentation and predict, based on data generated, the optimal ranges that will meet the target performance. This approach greatly facilitates the development of an ACS that, by design, is intended to be proactive. In other words, variables that are known or found to impact the quality of the reportable value are eliminated or limited to ranges where the impact is reduced to an acceptable level.

This is an important point in line with the QbD philosophy, which requires that quality be built into the product rather than relying solely on end-product testing. An ACS, in addition to placing controls on input variables, will also include a selection of system suitability tests that are intended to provide a means of verifying that the procedure is performing as expected. The combination of input controls and performance indicators, in the form of system suitability checks as components of a control strategy, is consistent with the principles described earlier in the QRM section. Thus, the input controls are aimed toward decreasing the probability of hazard occurrence, and the performance indicators in the form of system suitability are aimed toward increasing the detectability of hazards, thus minimizing the risk of harm to the quality of the reportable value.

Measures used to verify the adequate performance of an analytical procedure are, for example, %RSD for calibration standards and replicates, system suitability for chromatographic procedures, and resolution, plate count, or tailing factor. For an HPLC procedure, for example, replicate injections may be used to provide assurance that the system precision is satisfactory. Replicate sample or standard preparations provide assurance of the precision of the sample/standard preparation step, and a resolution check may be used to provide assurance that the accuracy of the procedure is not adversely affected by interference from other components in the sample. Ideally, system suitability checks should be designed to detect variation in the performance of a procedure in routine use. They should be based on an understanding of the risk and impact of variation, and the acceptance criteria used should be chosen to ensure that the measurement uncertainty does not exceed the TMU. A control sample (i.e., a homogenous and stable sample with a defined value for the attribute being measured) can also be used to provide confidence in the accuracy of the data generated.

How the ACS Applies to the Product Lifecycle

STAGE 2: QUALIFICATION

The second stage in the lifecycle approach to validation of analytical procedures involves confirming (or qualifying) that the procedure meets the requirements of the ATP (typically, the accuracy and precision of the reportable value), in the facility where the procedure will be routinely operated. Note that many of the important analytical characteristics, such as linearity, range, specificity, and sensitivity, will have been evaluated and characterized during stage 1. This qualification activity takes place once the initial ACS has been defined. Note that the result of the qualification activity may indicate that the ACS needs to be extended. An example of this could be a change to the replication strategy for samples and standards (see *Appendix*).

STAGE 3: CONTINUAL VERIFICATION

Once an ACS has been established and qualified as part of the analytical procedure, it is important that the performance of the procedure is maintained throughout the lifecycle (*16*). It is important therefore to have mechanisms for:

- Routine monitoring of the performance of the analytical procedure
- Controlling changes made to the analytical procedure

Routine Monitoring

It is beneficial to have a system for the collection and evaluation of information and data about the performance of the analytical procedure. This allows for detection of undesirable variability and trends. Many of the concepts and approaches described in *FDA Guidance for Industry: Process Validation: General Principles and Practices* (*17*) can also be applied to analytical procedures to ensure that the data they produce is valid throughout their lifecycle of use, as discussed in *FDA Guidance for Industry: Analytical Procedures and Methods Validation for Drugs and Biologics* (*18*). In addition, *Analytical Data—Interpretation and Treatment* ⟨1010⟩ (*19*) states that "Verifying an acceptable level of performance of an analytical system in routine or continuous use can be a valuable practice. This may be accomplished by analyzing a control sample at appropriate intervals, or using other means such as variation among the standards, background signal-to-noise ratios, etc. Attention to the measured parameter, such as charting the results obtained by analysis of a control sample, can signal a change in performance that requires adjustment of the analytical system" (*19*).

The aim of introducing a system for routine monitoring of procedure performance is to ensure that the analytical procedure is continuously producing reportable results that are fit for intended use. An analytical procedure can be considered fit for purpose when the requirements of the ATP are met. A routine monitoring program therefore needs to be designed to:

- Continually ensure that the reportable results produced by the procedure are fit for purpose
- Provide an early indication of potential procedure performance issues or adverse trends
- Ensure that any new understanding of the impact of variables on procedure performance is addressed in an updated ACS

Although system suitability checks are useful in establishing that a method is performing satisfactorily at time of use, having a mechanism for trending method performance over time is important in order to verify that the key variables impacting a procedure's performance are adequately understood and controlled. A program based on statistical process control techniques (*20,21*) is useful in order to trend the key indicators of procedure performance. However, it should be noted that the objective is conformance to the ATP

requirements, not necessarily to statistical rules. Trend plots of critical procedure performance indicators—such as resolution values, RSDs from system precision checks, results from routine testing, control or stability samples, or OOS or out-of-trend (OOT) investigations—can be established.

If the procedure is found to be producing inconsistent reportable values that do not meet the performance requirements defined in the ATP, or the root cause of performance issues identified from lab investigations indicates that a critical variable has not been identified or adequately controlled, the QRM process ACS should be reviewed and updated to reflect this new information.

Change Control

Effective qualification and monitoring of an analytical procedure provides confidence that the data generated are fit for purpose. In practice, however, during the lifecycle of a pharmaceutical product both the manufacturing process and the analytical procedure are likely to experience a number of changes through continuous improvement activities or the need to operate the method and/or process in a different environment. There are many drivers that may result in a change in the procedure. These include:

- Changes driven by the need to address new requirements for data quality (e.g., the tightening of specification limits or the need to control potential impurities from new suppliers of materials)
- Changes made to improve the quality of the data produced (e.g., where the measurement uncertainty is no longer acceptable or where new critical variables are identified)
- Changes that allow the data to be generated more quickly, more cost effectively, or by using more sustainable methods

These changes can range from small changes to the control strategy for the procedure to the development of a new analytical procedure based on a completely different technology. In order to ensure that any changes introduced during the lifecycle have no adverse impact on the fitness for purpose of the data, it is important to have effective processes in place to assess and control change.

A system of change control should be established and should provide the means for ensuring that all changes are recorded, evaluated, and approved prior to being implemented. In order to assess the impact of a change, it is important to first understand the requirements of the data. The ATP that defines the maximum acceptable TMU should be used as the basis against which to assess the change. The change control system should ensure that any changes are re-qualified as being able to meet the TMU requirements in the ATP, that work is completed, and that supporting documentation is updated and approved before the procedure is returned or introduced to routine use. Depending on the degree of change, the actions required to qualify the change will be different. Some examples are as follows:

a. A change in a method variable to a value that is within a range that was previously proven to produce fit-for-purpose data (e.g., changing an HPLC flow rate from 1.0 mL/min to 1.5 mL/min for an analytical procedure where a range of 1–2 mL/min was qualified during the method design stage). In this case, no additional experimentation is required to qualify the change.
b. Where the change is simply adding additional controls to an existing procedure (e.g., adding extra impurities to a test mix to help with peak identification). Again, this would not typically require any experimentation to qualify the change.
c. A change in a procedure variable to a value outside the range that was previously proven to produce fit-for-purpose data (e.g., changing a flow rate to 0.8 mL/min for the method used in the previous example). Changing to a method noise variable (e.g., a critical reagent source) would require a risk assessment. This should consider which procedure performance characteristics may be

impacted by the change and then should perform an appropriate method performance verification study to confirm that the change does not impact the method's ability to meet the ATP.

d. A change to a new procedure/technique would require performance of appropriate development, understanding, and qualification activities to demonstrate conformance of the new procedure to the ATP.
e. A change impacting the ATP (e.g., a specification limit change or the need to apply the procedure to measure levels of analytes not considered in the original ATP) would require an update to the ATP and a review of the existing procedure qualification data to determine whether the procedure will still meet the requirements of the new ATP. If not, a new or optimized analytical procedure or technology will be required and actions similar to those for example d. above would be required.
f. Sometimes it may be necessary to use the method in a new location (i.e., analytical transfer or implementation of compendial procedures). This type of change should be treated similarly to example c above. In this case, however, it is particularly important that effective knowledge transfer takes place between the established and new locations.

The level of qualification required to confirm a changed analytical procedure is producing fit for purpose data will depend on an assessment of the risk associated with the change. It is recommended that, for all changes, a risk assessment should be carried out to determine the appropriate level of (re-)qualification activities required. The aim of the (re-)qualification exercise is to provide confidence that the modified method will produce results that meet the criteria defined in the ATP. This may be assessed by considering the risk that the change in the method will have on the accuracy and the precision of the reportable result. Risk assessment tools can be used to provide guidance on what actions are appropriate to verify that the method is performing as required.

ACS for Different Sites

When an analytical procedure is going to be used at a new site, the laboratory will have to demonstrate that it can execute the procedure in a fit-for-purpose manner. Thus, the lab will have to show that when the analytical procedure is executed, the reportable result will meet the criteria established in the ATP. The preparation for the implementation of the new procedure will differ depending on how much knowledge is available—for example, an in-house method where the development findings, risk assessment conclusions, and subsequently established ACS are all known, compared with a compendial method where knowledge may not be available.

In the latter case, some of the QRM steps need to be verified, and as a result the ACS may need to be expanded. For example, additional environmental controls such as impact of exposure to light, temperature, and humidity; sample solution stability; or establishment of the site-specific replicate strategy need to be developed. The extent of the additional development/verification work will depend on how much knowledge is available to the receiving laboratory at the time of the qualification. Once the verification is complete, the new site will develop a qualification protocol or execute the existing qualification protocol to demonstrate that it is capable of generating a reportable result that meets the criteria established in the ATP, thus validating the original or the expanded ACS. After implementation, the new site should develop and implement the *Stage 3: Continual Verification* procedure as described earlier in this article.

CONCLUSION

The USP Validation and Verification Expert Panel believes that adopting a systematic approach to developing an ACS, in combination with the ATP (which is the driver for the development of the control strategy), will improve the performance of an analytical procedure. The use of KM and QRM tools will ensure that all work carried out during method design and development (stage 1) is value added, and should

ensure a successful qualification exercise at stage 2. Maintaining the control strategy when the method is in routine use (stage 3) through continually monitoring the performance of the procedure and applying good change control practices will ensure that the procedure maintains its "in-control" status.

This *Stimuli* article has described how an ACS can be developed and implemented to ensure that analytical procedures are robust throughout their lifecycle. The expert panel would appreciate any feedback on the suggested approach, as well as any alternative approaches for consideration.

APPENDIX

Replication Strategy

FORMAT OF THE REPORTABLE RESULT

By increasing the number of replications, one can reduce the variability of the mean (*19*), also known as the standard error. However, only the variance linked to the corresponding analytical step [precision level; ICH Q2 (*22*)] can be influenced (i.e., increasing the number injections and sample preparations will reduce the injection variance and sample preparation variance, respectively). Therefore, the level of replications, or format of the reportable result [see *Biological Assay Validation* ⟨1033⟩ (*23*)] can be used to optimize the precision of the reportable result as part of the ACS. On the same basis, the format of the calibration (i.e., the number of replications of the reference standard), can be optimized. An essential prerequisite for such an optimization is a precision or ruggedness study to estimate the relevant variance contributions with sufficient reliability. With respect to the format of the reportable result, the variance contributions linked to the replicate levels are the primary objective (i.e., injection/analysis variance, sample preparation variance, and between-run variance).

It is preferable to calculate the variance contributions using an analysis of variance (ANOVA). Two precision levels can be addressed by a one-way (or one-factor) ANOVA, such as repeatability and intermediate precision in the case of an intermediate precision study, or injection precision and repeatability in the case of a repeatability study with replicate injections. By applying multiple-factor ANOVA, one can separate the variances of multiple steps of an analytical procedure, or of several variation factors. For example, if duplicate injections are performed in an intermediate precision study, three precision levels (i.e., system precision, repeatability, and intermediate precision) can be calculated by using a two-factor ANOVA [see Koller (*25*), or statistical textbooks].

OPTIMIZING THE PRECISION OF THE REPORTABLE RESULT

As mentioned above, one can reduce the variability of the reportable result by increasing the number of replicates, but only for the corresponding variance contributions (*19*). *Equation 1* below has been extended to include all precision levels. In contrast to bioassays, in chemical analysis the number of runs (k) is usually one. In the case of a single determination (injection), $k = n = m = 1$, the precision of the reportable result equals the intermediate precision. The two-term equation with the repeatability variance is used when no repeated analysis of the same sample solution is possible (e.g., titration of solids).

$$s_{RR}^2 = \frac{s_b^2}{k} + \frac{s_p^2}{k*n} + \frac{s_{sys}^2}{k*n*m} = \frac{s_b^2}{k} + \frac{s_r^2}{k*n} \quad [1]$$

s^2 = variance between series (b), of repeatability (r), of sample preparation (p), and of system (sys)
k = number of runs using independent reference standard analysis (calibration)
n = number of sample preparations
m = number of injections/analysis of the same solution

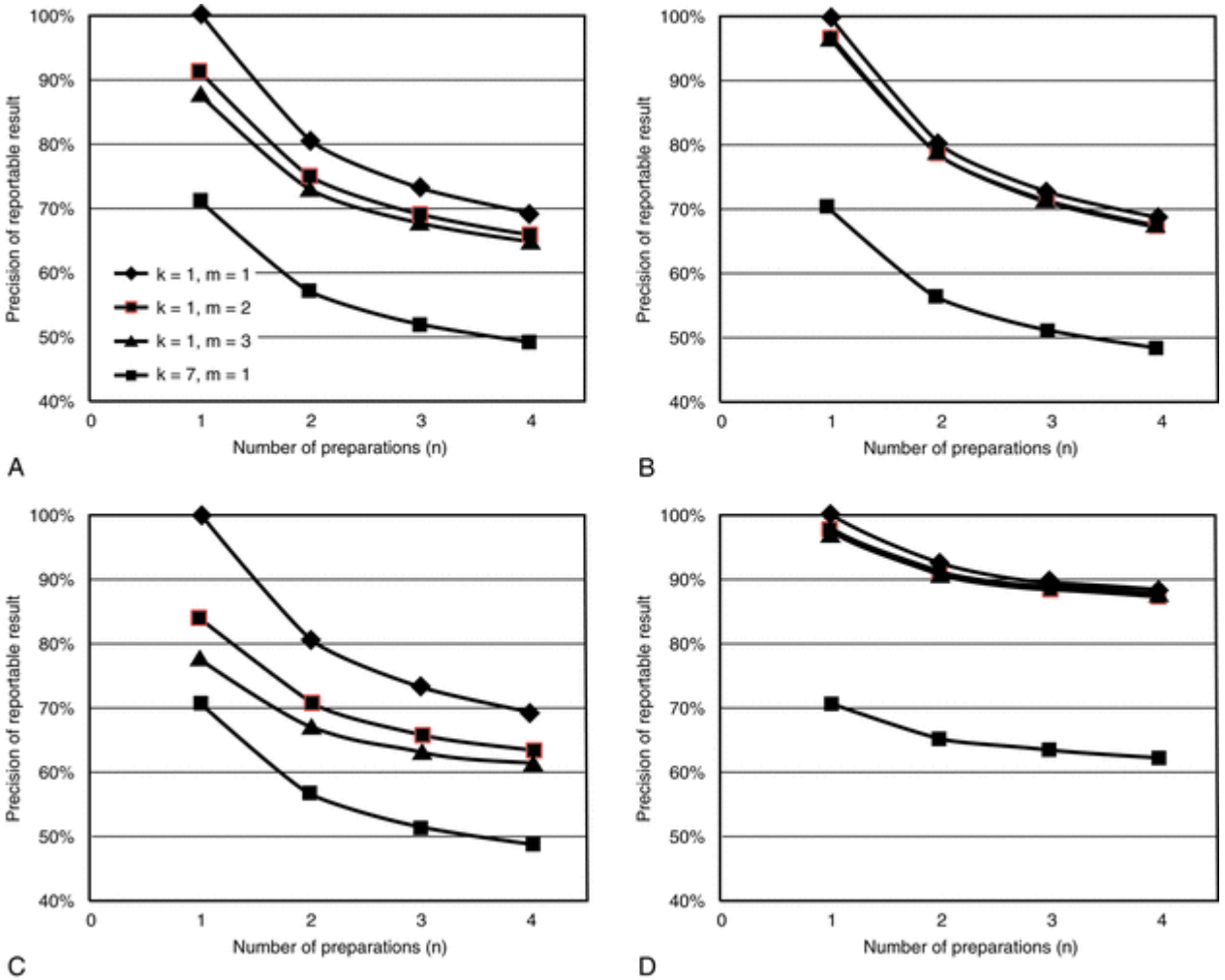


Figure 1. Precision of the reportable result for various formats, dependent on the relative variance contributions. Injection variance: sample preparation variance: between-run variance = 35%:35%:30% (A); 10%:60%:30% (B); 60%:10%:30% (C); and 10%:20%:70% (D).

Using *Equation 1*, it is possible to make a scientifically based decision on the required or necessary number of determinations, depending on the corresponding weight of the variance contributions (see *Figure 1*). If the variance contribution of injection is small, increasing the number of injections will have a negligible impact on the precision of the reportable result, and hence a single injection is sufficient (*Figure*

1A). In the case of a considerable fraction of the injection variance, as is typical for impurity determinations and often for drug substance assays, the precision can be increased by repeated injections (*Figure 1B*), maintaining a single sample preparation for the format of the reportable result.

A large between-series variance can only be offset by increasing the number of series for each reportable result, which is often done in biological assays, but not in chemical analysis. Because the improvement of precision is only proportional to the square root of the replicate number, the "gain" will get smaller. Therefore, a balance between effort and gain should be sought, with the primary evaluation based on the precision required from the application, as established in the ATP. An appropriately justified reportable result will achieve a better estimate of the true value, and thus guarantee a more reliable decision. This should by no means be confused with hiding variability. Of course, it has to be verified that the actual routine variability is as expected.

However, the format of the reportable result is just one aspect of the ACS. Even with a single sample preparation as the reportable result, one may decide to analyze more samples, for example, as a precaution to identify special-cause errors. Besides this "statistical" optimization of the precision, the knowledge of the variance contributions can also be used as a starting point to achieve method optimization. For example, a large variance of sample preparation differing between series may be caused by different operators and could be reduced by providing better instructions and/or controls. Further sub-analysis of between-run variation factors, such as analyst, equipment, reagents, etc., may also be used to limit variability by using more detailed instructions or restrictions as part of the ACS, if needed.

OPTIMIZATION OF THE CALIBRATION FORMAT

In the case of external calibration, the variability of the reference standard analysis is one of the factors (besides instrument, operator, reagents, etc.) that affects the between-series variance contribution at the intermediate precision/reproducibility level. Therefore, the precision of the reportable result is only valid for the very calibration format used in the precision study. Of course, repeating the whole precision study with various calibration formats would be very time consuming. Instead, the number of reference standard replicates can be optimized using a statistical approach also based on variance contributions, which can largely be obtained from the original precision study (see *Equation 2*) [for details, see Ermer and Agut (*26*)]. Note that the uncertainty of the declared reference standard content cannot be influenced by the number of determinations. If relevant, it has to be considered as an additional, fixed variance term in *Equation 2*.

$$CV^2_{RR^*} = CV^2_{RR} - CV^2_{RP} \cdot \left(\frac{1}{n_{RS}} - \frac{1}{n_{RS^*}} \right) - CV^2_I \cdot \left(\frac{1}{n_{RS} * m_{RS}} - \frac{1}{n_{RS^*} * m_{RS^*}} \right) \quad [2]$$

CV^2_{RP} and CV^2_I = squares of reference standard preparation coefficient of variation (relative standard deviation) and injection/system CV, respectively
n_{RS}, m_{RS} = number of injections and preparations (i.e., format) of reference standard analyses used for the precision study to obtain intermediate precision
n_{RS*}, m_{RS*} = number of preparations of reference standard analyses for an alternative format

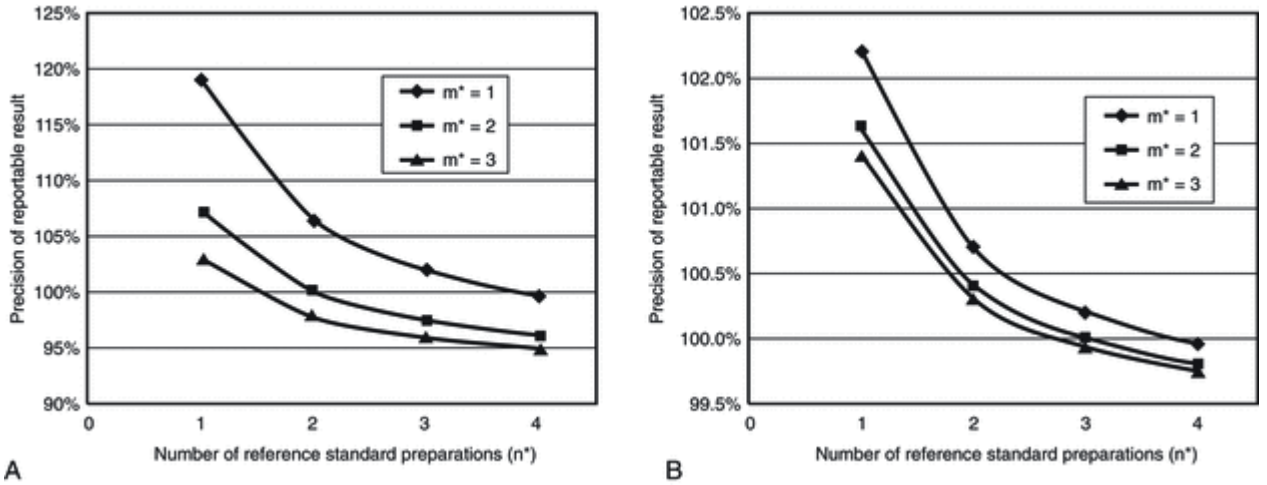


Figure 2. Dependence of intermediate precision on the format of calibration. The calculated precisions for alternative calibration formats are normalized with respect to the intermediate precision obtained in the precision study. The following relative standard deviations for the reference standard were used: API, example A: CV_{RR} = 0.76%, CV_{RP} = 0.14%, CV_I = 0.58%; Tablet, example B: CV_{RR} = 1.42%, CV_{RP} = 0.35%, CV_I = 0.22%.

In the case of a larger number for the new calibration format, the original relative standard deviation of the reportable result will decrease according to the weight of the reference standard variances. For a smaller number, the difference of the reciprocal numbers becomes negative, and hence the original relative standard deviation would increase. The impact of the format of the calibration depends on the contribution of the reference standard variances to the overall variability. The larger this contribution, the larger is the sensitivity to format variations (*Figure 2A*). On the other hand, in the case of a small contribution, the number of reference standard analyses can be minimized without much impact on the reportable result precision. For the example shown in *Figure 2B*, a single reference standard preparation and injection would not affect the precision of the reportable result significantly. In the case of impurity determinations also, the concentration dependence of the precision should be considered, defining a sufficiently large reference standard concentration to ensure an optimized precision (*19,22–27*).

REFERENCES

1. International Conference on Harmonisation. Q9: quality risk management. Geneva: International Conference on Harmonisation; November 2005. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q9/Step4/Q9_Guideline.pdf. Accessed 2 August 2016.
2. Barnett K, McGregor PL, Le Blond D, Weitzel J, Walfish SL, Ermer J, et al. Analytical target profile (ATP): structure and application throughout the analytical lifecycle. *Pharm Forum*. 2016;42(6).
3. International Conference on Harmonisation. Q10: pharmaceutical quality system. Geneva: International Conference on Harmonisation; June 2005. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q10/Step4/Q10_Guideline.pdf. Accessed 2 August 2016.

4. International Conference on Harmonisation. Quality implementation working group on Q8, Q9 and Q10. Questions & answers (R4). Geneva: International Conference on Harmonisation; November 2010. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q8_9_10_QAs/Q-IWG_Q_A_R4_Step4_Nov.2010.pdf. Accessed 2 August 2016.
5. International Conference on Harmonisation. Training programme for Q8/Q9/Q10: presentations. http://www.ich.org/products/guidelines/quality/training-programme-for-q8q9q10/presentations.html. Accessed 2 August 2016.
6. Canadian Association for Laboratory Accreditation (CALA). Measurement uncertainty arising from sampling: the new Eurachem guides. The New CALA course: uncertainty in sampling and compliance assessment and why you should take it. Ontario: CALA; 2012. http://www.cala.ca/t_nw_MU_from_sampling.pdf. Accessed 2 August 2016.
7. Nickerson B, ed. *Sample Preparation of Pharmaceutical Dosage Forms: Challenges and Strategies for Sample Preparation and Extraction*. Berlin: Springer; 2011.
8. Burgess C, Curry P, LeBlond DJ, et al. Fitness for use: decision rules and target measurement uncertainty. *Pharm Forum*. 2016;42(2).
9. Subcommittee E11.20 on Test Method Evaluation and Quality Control. ASTM E2655-14, Standard guide for reporting uncertainty of test results and use of the term measurement uncertainty in ASTM test methods. West Conshohocken, PA: ASTM International; 2014.
10. Ellison SLR, Williams A. *Eurachem/CITAC Guide: Quantifying Uncertainty in Analytical Measurement*. 3rd ed. Leoben, Austria: Eurachem; 2012. www.eurachem.org/images/stories/Guides/pdf/QUAM2012_P1.pdf. Accessed 2 August 2016.
11. Bettencourt da Silva R, Williams A, eds. *Eurachem/CITAC Guide: Setting and Using Target Uncertainty in Chemical Measurement*. 1st ed. Leoben, Austria: Eurachem; 2015. www.eurachem.org/images/stories/Guides/pdf/STMU_2015_EN.pdf. Accessed 2 August 2016.
12. Barnett K, Doyle K, Wang K, Morgado J, Harwood J. Applying quality by design principles to analytical methods to gain enhanced method understanding. *Amer Pharm Rev*. 2015. http://www.americanpharmaceuticalreview.com/Featured-Articles/174279-Applying-Quality-by-Design-Principles-to-Analytical-Methods-to-Gain-Enhanced-Method-Understanding/. Accessed 2 August 2016.
13. Borman PJ. Application of AMQbD within GlaxoSmithKline. Presented at the IFPAC 2014 Annual Conference; January 24, 2014; Arlington, VA. http://www.infoscience.com/JPAC/ManScDB/JPACDBEntries/1394040327.pdf. Accessed 2 August 2016.
14. Borman PJ, Chatfield MJ, Damjanov I, Jackson P. Method ruggedness studies incorporating a risk based approach: a tutorial. *Anal Chim Acta*. 2011;703:101–113.
15. ICH Expert Working Group. Quality risk management: ICH Q9. Annex I: methods & tools. http://www.pmda.go.jp/files/000156774.pdf. Accessed 2 August 2016.
16. Nethercote P, Burgess C. Chapter 8: continued method performance verification. In: Ermer J, Nethercote P, eds. *Validation in Pharmaceutical Analysis: A Guide to Best Practice*. 2nd ed. Weinheim, Germany: Wiley-VCH; 2015:377–406.
17. Food and Drug Administration. Guidance for industry. Process validation: general principles and practices. Rockville, MD: Food and Drug Administration; January 2011. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070336.pdf. Accessed 2 August 2016.
18. Food and Drug Administration. Guidance for industry. Analytical procedures and methods validation for drugs and biologics. Rockville, MD: Food and Drug Administration; July 2015.

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM386366.pdf. Accessed 2 August 2016.

19. United States Pharmacopeia. ⟨1010⟩ Analytical data—interpretation and treatment. In: *USP 39–NF* 34. Rockville, MD: United States Pharmacopeial Convention; 2016:767.
20. Deming SN. Statistics in the laboratory: control charts, part 1. San Francisco, CA: American Laboratory; 2016. http://www.americanlaboratory.com/914-Application-Notes/182490-Statistics-in-the-Laboratory-Control-Charts-Part-1/. Accessed 2 August 2016.
21. Deming SN. Statistics in the laboratory: control charts, part 2. San Francisco, CA: American Laboratory; 2016. http://www.americanlaboratory.com/913-Technical-Articles/185070-Statistics-in-the-Laboratory-Control-Charts-Part-2/. Accessed 2 August 2016.
22. International Conference on Harmonisation. Q2(R1): Validation of analytical procedures: text and methodology. Geneva: International Conference on Harmonisation; November 2005. http://www.ich.org/products/guidelines/quality/article/quality-guidelines.html. Accessed 2 August 2016.
23. United States Pharmacopeia. ⟨1033⟩ Biological assay validation. In: *USP 39–NF 34*. Rockville, MD: United States Pharmacopeial Convention; 2016:862.
24. International Organization for Standardization. 5725-2:1994, Accuracy (trueness and precision) of measurement methods and results–part 2: basic method for the determination of repeatability and reproducibility of a standard measurement method. Geneva: International Organization for Standardization; 1994.
25. Koller K, Wätzig H. Precision and variance components in quantitative gel electrophoresis. Electrophoresis. 2005;26:2470–2475.
26. Ermer J, Agut C. Precision of the reportable result. Simultaneous optimisation of number of preparations and injections for sample and reference standard in quantitative liquid chromatography. *J Chromatogr A*. 2014;1353:71–77.
27. Ermer J. 5.2.5.2. Optimization of the calibration format. In: Ermer J, Nethercote PW, eds. *Method Validation in Pharmaceutical Analysis. A Guide to Best Practice*. 2nd ed. Weinheim, Germany: Wiley-VCH; 2015:97–100.

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Analytical Target Profile: Structure and Application Throughout the Analytical Lifecycle

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ABSTRACT In this *Stimuli* article, the USP Validation and Verification Expert Panel discusses how the development of an analytical target profile (ATP) can be achieved and how the ATP is used in relation to the analytical procedure in the three stages of the lifecycle. The importance of the ATP was briefly discussed in a previous *Stimuli* article, *Lifecycle Management of Analytical Procedures: Method Development, Procedure Performance Qualification, and Procedure Performance Verification* (*PF* 39(5) [Sept.–Oct. 2013]). The 2013 *Stimuli* article described how the ATP captures the quality attributes of the reportable value, which reflects the fitness for purpose of the analytical procedure and connects all stages of the procedure lifecycle. Examples of ATPs for assays and an impurity testing were provided for illustrative purposes. The ATP is discussed further in this article, including its development, the linkage between the ATP and analytical control strategy, and application to each of the three analytical procedure lifecycle stages: design, qualification, and performance verification. This article is intended to be a companion to a separate *Stimuli* article that discusses application of analytical procedures and establishes a control strategy for analytical procedures (see *Analytical Control Strategy* in this issue of *PF*). Although the focus is on compendial procedures, some concepts may also be applied to other types of procedures as appropriate.

This article will consider the following questions related to the ATP:

- What is an ATP, and why is it useful?
- How can the ATP criteria (data quality attributes) be established?
- How can an ATP be applied during the three stages of the procedure lifecycle?

This article discusses an approach that may be used to determine an ATP, which leads to a better understanding of total analytical error associated with the result produced by the procedure. Holding the reportable value produced by the analytical procedure accountable to the ATP can promote development of a more in-depth control strategy through better control of risks, allowing procedures to perform more consistently throughout the lifecycle, particularly when used in new environments or as technologies advance. Specific examples of an ATP for the assay of a solid dosage form (tablet) are included.

Comments are requested, including suggestions for alternative ATP approaches.

INTRODUCTION

The current approach to development, validation, verification, and transfer of analytical procedures has served the industry well. The lifecycle approach—comprised of the development (stage 1), qualification (stage 2), and monitoring of the performance of analytical

procedures (stage 3)—is an extension of the current guidance, taking advantage of our learnings from quality by design (QbD).

Application of lifecycle concepts to analytical procedures is optional; however, it does provide a framework for enhanced understanding and control of the variability associated with the results generated by the analytical procedure.

This article discusses the ATP concept in greater detail and presents two options for an ATP statement, as well as discussing how such statements may be assessed. It is important to note that the approach provided here is intended as an example and is not meant to suggest a single approach or suggest that current approaches are in need of complete reform. Other approaches that have more or less rigor may also be appropriate. The main point of this article is to illustrate the benefits of applying the ATP concept to better understand and control measurement uncertainty.

What Is the ATP and Why Is It Useful?

The ultimate purpose of an analytical procedure is to generate a test result, and based on this result, to make a decision about the parent body, sample, batch, or in-process intermediate from which the laboratory sample is obtained. The proposed lifecycle approach includes consideration of the target measurement uncertainty (TMU) (*1*) and the bias simultaneously. TMU is a more comprehensive term than the traditional term "precision" to represent random errors, and bias is a term traditionally used to represent systematic errors or accuracy. These terms (uncertainty and bias), when examined holistically, can be considered to represent the TMU associated with the reportable value generated by the procedure.

A fundamental component of the lifecycle approach is establishing a predefined objective that stipulates the performance requirements for the analytical procedure. This is captured in the ATP.

The ATP states the required quality of the results produced by a procedure in terms of the acceptable error in the measurement; in other words, it states the allowable TMU associated with the reportable value.

Because the ATP describes the quality attributes of the reportable value, it is applied during the procedure lifecycle and connects all of its stages.

As described in a recent *Stimuli* article [see *Fitness for Use: Decision Rules and Target Measurement Uncertainty* in *PF* 42(2)] (*2*), the criteria captured in the ATP should reference the product or output of the procedure, i.e., the results, rather than performance characteristics of the analytical procedure. The term performance characteristics refers to the performance aspects of the procedure itself (rather than the output); performance characteristics are described in the FDA pharmaceutical validation guidelines; *Validation of Compendial Procedures* ⟨1225⟩; and International Council for Harmonisation (ICH) Q2(R1). Validation practices are frequently treated as a check-box exercise in which analysts compare the validation results to validation criteria—often these are default criteria—to satisfy compliance objectives. Less consideration may be given to understanding total measurement error and how it will influence the decisions to be made, for example the decision to accept or reject a batch.

Currently, the pharmaceutical industry develops and validates procedures in alignment with ICH and USP guidance. The guidance recommends setting criteria and separately assessing performance characteristics that are good indicators of the performance of an analytical procedure: accuracy, precision, linearity, specificity, sensitivity, and robustness. Although these indicators are important to

understand during development, they do not provide a direct measure of the quality, or the error associated with the results generated by the procedure (*3*). It is common practice to establish default criteria for these validation elements, although the rationale for these criteria is not always transparent. These default validation criteria are often established based on several considerations including product specifications, typical variability of methodology used to characterize drug substances and products, and regulatory feedback. However, they often lose their connection to the ultimate purpose of an analytical procedure, which is generating results upon which decisions are based. Identifying the required output in terms of the final result of the analytical procedure in an ATP statement provides a target for development and helps to ensure that the procedure is developed toward predetermined requirements that are directly linked to the intended use of the procedure and the specifications. Hence, results will be generated during routine testing with an understanding of the TMU associated with them, as well as the effect on decisions made with those results.

All procedure performance characteristics, including the validation elements discussed above, will ultimately be consolidated in the attributes of the final result as illustrated in *Figure 1*.

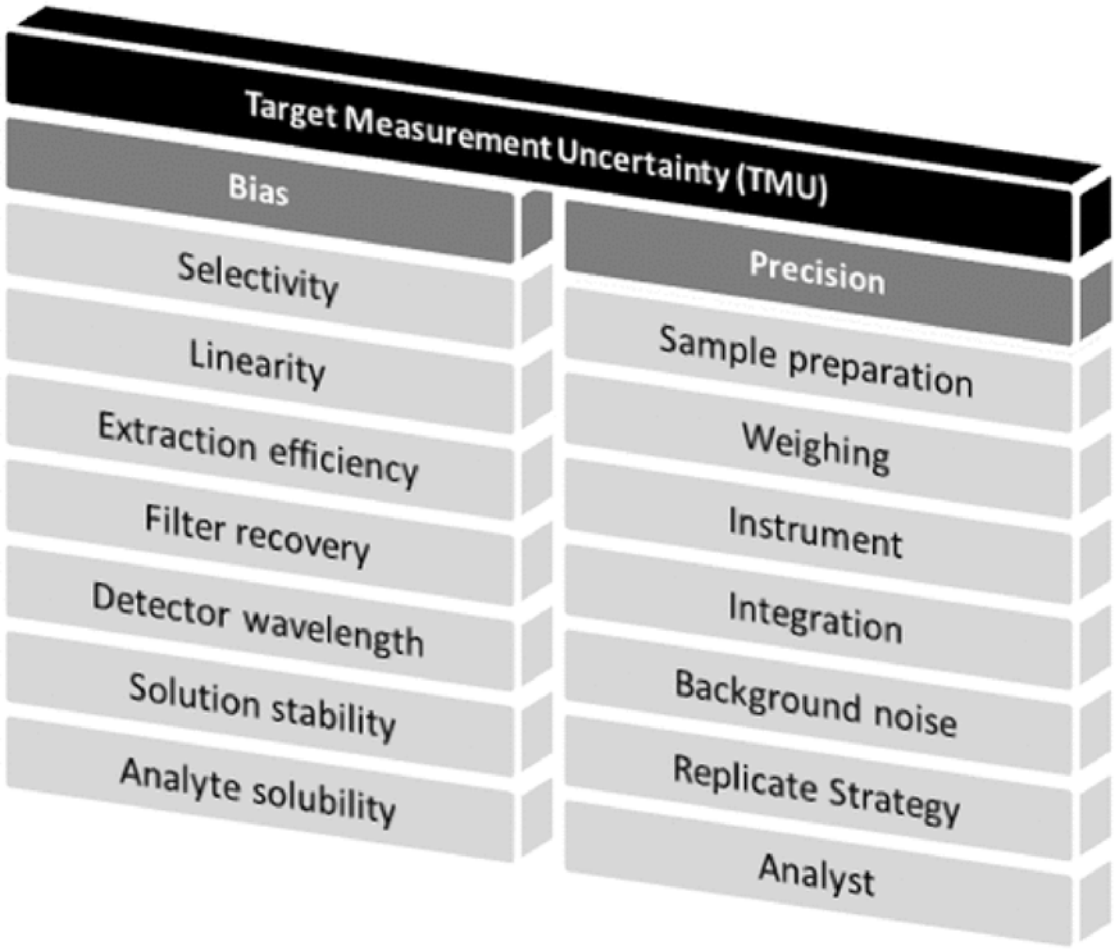

Figure 1. Consolidation of attributes contributing to TMU through bias and precision.

Before considering the determination of the ATP, it is important to discuss the concept of a true value versus a measured value. Each result has a corresponding actual value, called a true value. The true value cannot be known unless a sample was measured an infinite number of times, which is not practical. In practice, the true value is estimated by obtaining a measurement; this is called the measured value. It is the measured value that is used for the final result. Therefore, the acceptable measurement error, which describes the difference between the true value and the measured value, is considered in the TMU.

How Can the ATP Criteria Be Established?

The ATP should establish criteria for the TMU of the test results that are used to make a decision about a batch (reportable value). As a first step in determining ATP criteria, the product specification or target (draft or final) should be identified. For these examples, we will assume our tablet drug product has an assay specification of 95.0%–105.0%, which is common for solid oral dosage forms.

There are several ways to structure an ATP, and two examples are provided here. The first example (ATP #1) is aligned with current USP and ICH guidances, with the important improvement that the performance requirements are linked to the reportable value. The second example (ATP #2) is based on the ATP that appeared in the initial *Stimuli* article [see *Lifecycle Management of Analytical Procedures: Method Development, Procedure Performance Qualification, and Procedure Performance Verification* in *PF* 39(5)] and references a more rigorous statistical approach compared to our current industry guidance. Either of these example ATPs may be appropriate, depending on the circumstances in which it is applied and how the criteria are established and justified.

When determining an ATP, the following should be considered:

- Sample to be tested
- Matrix in which the analyte will be present
- Range of analyte content (or concentration if appropriate). Ideally, this should reference the content in the product (e.g., drug substance, drug product, or excipient), not the amount of analyte in the sample solution subjected to the analytical measurement)
- Allowable error for the measurement as assessed through bias and precision
- Allowable risk of the criteria not being met (proportion of results that are expected to be within the acceptance criteria)
- Confidence that the measurement uncertainty and risk criteria are met

The ATP considers the acceptable level of risk of making an incorrect decision with the reportable values. Setting decision rules (*1*) may assist in this area, but is not always necessary. As a first consideration, the acceptable level of risk should be linked to patient safety and product efficacy, as well as the risk of erroneously accepting a batch that does not meet specifications. Manufacturer risk, i.e., the risk of erroneously rejecting a lot that meets specifications [a false out-of-specification (OOS) result] can also be considered when criteria for risk are established. In many cases, pharmaceutical specifications are established based on a quality rationale related to the capability of processes and analytical procedures, rather than clinical relevance. In these cases, manufacturer risk may be the main consideration when establishing an acceptable level of risk. When considered in this way, the ATP is independent of the technique and can be used to guide technique selection and procedure development in the design and understanding stage.

Because the ATP describes the quality of the reportable value, the current ICH and USP validation guidance can be incorporated into an ATP as shown below for a drug product assay in *Example 1*.

EXAMPLE 1: ATP #1

The procedure must be able to accurately quantify [drug] in the [description of test article] in the presence of [*x, y, z*] with the following requirements for the reportable values: Accuracy = 100% ± *D*% and Precision ≤ *E*%.

Note that [*x, y, z*] are the specified impurities and excipients.

Advantages of this approach to an ATP are:

- The ATP is easy to understand, the calculations are relatively straightforward, and the data are easy to assess for ATP conformance by nonstatisticians.
- The ATP includes criteria for accuracy and precision of the reportable value and is therefore linked to the quality of the reportable values. In current approaches, criteria for accuracy and precision are often established based on generally accepted industry practices using default criteria. However, in a QbD approach, these criteria should be aligned with the specification and the product and process needs.
- The QbD approach encourages understanding and control of sources of variability (defined control strategy).

Limitations of this approach include:

- Accuracy and precision are assessed separately so that TMU of the results is not explicitly defined.
- This approach does not quantify the risk of making a wrong decision by including probability and confidence criteria. However, although the level of risk is not transparent, risk can be controlled through alignment of specifications and accuracy/precision criteria such that reportable values that are within specification have a low probability of being on an edge of failure with respect to clinical relevance.

EXAMPLE 2: ATP #2

A simplified version of the ATP that was described in the initial *Stimuli* article of *PF* 39(5) is shown below as ATP #2. This example contains criteria for TMU (±*C%*) and is directly linked to the results generated by the procedure.

The procedure must be able to quantify [analyte] in the [description of test article] in the presence of [*x*, *y*, *z*] so that the reportable values fall within a TMU of ± *C%*.

The ATP inputs for [analyte], [description of test article], and [*x, y, z*] can be specified.

C describes the acceptable TMU. It considers the acceptable difference between the measured value and the target value and can be established based on a fraction of the specification range.

Assessment of Different ATP Scenarios

There are several ways to assess TMU, and one example is shown here. In this example, a two-sided beta-content tolerance interval (TI) approach is used to model ATP criteria to understand the effect of the various inputs on measurement uncertainty and its consequences for

the design of the qualification study in stage 2. It should be noted that this is simply one way to assess measurement uncertainty. Other approaches, including other statistical approaches (*4*) and different criteria and supporting rationales, may also be acceptable (*5*,*6*).

The TI is a statistical concept that describes the proportion or fraction of future results that will fall within a given range with defined level of confidence. The TI concept can be used to assess TMU, which can be compared to ATP criteria. To establish TMU for the ATP, ideally the TMU should be a fraction of the specification range. In this case, 60% of the specification range (95%–105%) is chosen so that TMU is ±3.0%. This is acceptable because the specifications for pharmaceutical product assays are often based on method and manufacturing capabilities, and in this case the drug product assay specification is well within clinically relevant requirements. In this example, we expect batches to be manufactured to a nominal target value of 100% of label claim. Therefore, the main risk is to the manufacturer in that the procedure may generate OOS results that may lead to rejection of a batch that is actually acceptable. Associating a TMU with the reportable value will help with making the correct decision and aid in the assessment of OOS results.

The above values are inserted into the ATP statement, which becomes:

The procedure must be able to quantify [analyte] in the [description of test article] in the presence of specified impurities and excipients so that the reportable values fall within a TMU of ±3.0%.

Once the ATP criteria have been determined, the next step is to model the ATP to determine its feasibility in terms of the selected technology and intended use of the procedure. The modelling step provides the chemist with an idea of how accurate and precise the procedure needs to be, hence it provides an orientation guide to develop the procedure and associated control strategy. In this example, the ATP is modelled using a two-sided beta-content tolerance interval approach calculator available at http://statpages.info/tolintvl.html.

Using a TI approach and based on the ATP statement, one can explore different scenarios that consider the proportion of results that lie within a given range of the true value, the associated confidence, the magnitude of procedure bias, and the maximum allowed precision. In this example, the proportion is set at 90% because it is desirable for a high proportion of results to meet the TMU requirement. Note that the TI calculator above can only determine TIs for a single series. In this case, a series is a single run with a given analyst and instrument on a given day. Therefore, the maximum allowed precision calculated in this way corresponds to repeatability. This target can be used to assess the general feasibility, and as a guide for the development phase. The repeatability target chosen from the scenarios given in *Table 1* is based on six determinations. This approach is loosely aligned with ICH recommendations and leaves sufficient flexibility for the intermediate precision factors, which are considered in the final qualification study in stage 2 of the lifecycle approach.

Because we are dealing with drug product for which we cannot know the true value of the active content due to variability in the production process, for the purposes of the ATP we assume our true value is the target value of 100% label claim.

The following scenarios are evaluated using the TI calculator:

- Confidence scenarios: 90% vs. 50%
- Bias scenarios: 0% vs. 1%
- Number of determinations (repeatability): 6 vs. 12 replicates

Table 1 shows the outcome of modeling these scenarios. With the exception of *Scenario 4*, all of these examples have TIs within the range of −3.0 to +3.0, which means they are potentially capable of meeting the TMU criteria defined in the ATP of ±3.0%. The precision values shown in Table 1 are intended as estimates to guide method design and optimization of the control strategy during stage 1 and are not intended as requirements for subsequent intermediate precision studies that will be used for qualification (this will be discussed later in stage 2.)

Note—It is a useful exercise to use the website tool to create various scenarios and explore the relationships between precision, bias, proportion, and confidence. In this example, six determinations are chosen because this aligns with common industry practice.

Table 1. ATP Scenarios

	Scenario 1	Scenario 2	Scenario 3	Scenario 4
Proportion	90%	90%	90%	90%
Confidence	50%	50%	90%	50%
Bias[a]	1.0%	0%	0%	3.0%
Determinations	6	6	6	6
Estimated maximum %RSD (repeatability)	1.1%	1.6%	1.0%	2.0%
Tolerance interval	−1.0 to +3.0	±3.0	−1.0 to +3.0	−1.8 to +6.8

[a] For the purpose of the web link, insert the bias (difference from the target value) in the box for the mean value.

In Table 1, *Scenarios 1* and *2* are identical except for the 1% bias in *Scenario 1* while *Scenario 2* has 0% bias. The presence of 1.0% procedure bias in *Scenario 1* results in a decrease in the estimate of the maximum relative standard deviation (%RSD) from 1.6% (*Scenario 2*) to 1.1% (*Scenario 1*) for six determinations to maintain the same level of measurement uncertainty. These scenarios highlight the relationship between bias and precision, i.e., if bias exists, the maximum allowable %RSD will decrease to account for the increase in bias.

Scenario 3 shows an example having a high degree of confidence (90%) and proportion (90%). In this scenario, the corresponding maximum allowable %RSD is 1.0% as demonstrated with six determinations when there is 0% procedure bias. This level of combined precision and bias may be challenging to achieve during routine use of drug product assays.

To put this into perspective, the current approach, as described in ICH Q2, has separate requirements for accuracy and precision leading to wider criteria for total variability than may be apparent. An example would be an assay with acceptance criteria of 3.0% accuracy and 2.0% RSD (commonly applied default criteria for accuracy and repeatability studies) (*2,3*). These individual acceptance criteria could be considered acceptable using the current approach.

As shown in *Scenario 4*, this would produce a TI of −0.8% to 6.8% at 50% confidence with 90% proportion based on six determinations. This corresponds to a maximum TMU of 6.8%. Although this example is oversimplified from a statistical perspective, it illustrates how the proposed ATP approach can be used to control the measurement uncertainty to a defined maximum level, with bias and precision evaluated holistically.

In this example, *Scenario 2* in *Table 1* is chosen as a guide for procedure design, targeting: a) <1.6% RSD for repeatability, and b) zero or negligible bias (ideally, any bias due to systematic errors will be resolved during method development, therefore the target bias for the procedure is selected as 0%). An RSD of 1.6% is reasonable and generally achievable for a drug product tablet procedure. Note that this is a precision estimate to use as a guide during development of the procedure and control strategy. The final tolerance interval will be calculated from the results of the intermediate precision study during the qualification stage 2.

Proportion is set at 90% to reflect the desire for a high proportion of results to fall within the TMU. A value of 50% confidence is chosen as it aligns with typical industry practices.

Advantages of the approach described by ATP #2 include:

- It is consistent with the spirit of ICH and USP guidance and the metrological approach.
- It increases the chemist's awareness of the relationships between precision, bias, proportion, confidence, and number of determinations.
- Accuracy and uncertainty are assessed holistically so that TMU is explicitly constrained.
- It considers the risk of making a wrong decision by including criteria for the proportion of the results that should meet ATP criteria with a level of confidence.
- Established approaches described in Eurachem (*1*) and ISO (*7*) guidances can be applied to determine TMU.

Challenges and limitations of this approach are:

- This is a different way of thinking for analytical chemists. It requires the use of statistical tools/software, and statisticians may be needed to support analytical chemists and/or to perform these assessments, particularly for design of the qualification study in stage 2.
- More samples than is the current practice may be needed to demonstrate adherence.
- This approach may be challenging to implement with some of the tighter industry specifications (for example, the API assay) without decreasing the probability and confidence requirements to a level that some may find undesirable. Note that this is not an indication that current procedures are unsuitable to ensure patient safety but is instead the result of specifications that are established based on quality arguments related to process and procedure capability.

There are situations when an analyst may not have enough information to finalize the ATP criteria, such as when specifications have not yet been finalized. In these cases, an ATP can be established based on target specifications, prior knowledge, or the intended use of the procedure. Any changes to the ATP should trigger an assessment of the appropriateness of the analytical procedure. The ATP should not be changed based solely on procedure capability.

How Can an ATP Be Applied During the Three Stages of the Procedure Lifecycle?

STAGE 1: PROCEDURE DESIGN, DEVELOPMENT, AND UNDERSTANDING

ATP criteria should be established before starting procedure design activities. Note that ATP criteria are independent of the technique, allowing an analyst to select any technique that is capable of providing the performance needed to meet the ATP criteria.

When the need for a monograph procedure is identified, relevant information should be gathered before conducting laboratory studies. This information may include known chemical structures, solubility, reactivity, and stability of the molecules of interest. A literature search may also be useful to find out how the procedure has been applied or modified by others. The intended purpose of the procedure for routine use must always be considered. Any relevant information identified during the knowledge-gathering stage, such as criteria for run time, equipment type, and others, are also considered during the design and development stage. However, this information is not captured in the ATP.

By following the current approach as outlined in ICH and USP guidance documents, it is relatively straightforward to translate validation criteria into procedure performance characteristics (e.g., specificity, sensitivity, and others) to guide procedure development activities. For example, validation characteristics such as specificity, linear range, and sensitivity are evaluated as part of the development activities, often by using default validation criteria as a reference. Thus, there is a clear and direct connection between validation guidance and procedure development activities when following the current approach.

In the lifecycle approach, relevant performance characteristics should be assessed as described in ICH Q2(R1) and ⟨1225⟩ during stage 1. The connection between the analytical performance characteristics described by ICH Q2(R1) and ⟨1225⟩ and the criteria for TMU captured in the ATP may not be apparent because some of the analytical performance characteristics are not cited directly in the ATP. ICH and USP analytical performance characteristics are important and necessary to meet the level of quality of the data stipulated in the ATP. In other words, if the procedure does not have a suitable calibration model, appropriate specificity, sensitivity, and others, the ATP (which describes the allowable TMU) will not be met. Targets for these performance characteristics can be established based on ATP criteria to support procedure design activities and can be included in the control strategy.

It is important to consider all steps in the analytical procedure during the procedure design stage, including the preparation conditions for standards and test samples. Sample preparation conditions are frequently a source of procedure variability and/or bias and should be confirmed through systematic extraction studies to ensure robust, rugged, and complete extraction (*8*).

During stage 1, system suitability and other method controls in the monograph (if available) are assessed. A preliminary assessment of the ability of the procedure to yield results with the required TMU as stated in the ATP is performed using real and/or spiked samples. On the basis of these studies, additional or different procedure controls can be proposed as needed.

Additional controls based on risk assessments and multifactor studies may also be added at this stage to ensure that the operation of the procedure is adequate for its intended use. It is important to investigate sources of variability and systematic bias during stage 1 so they may be eliminated or controlled during routine use of the procedure. This is discussed in more detail in the companion *Stimuli* article, *Analytical Control Strategy* (*9*).

If the results generated during subsequent studies fail to meet the ATP criteria, the design stage can be revisited, targets for performance characteristics can be refined, and design activities can be continued based on the refined targets. Note that returning to the design stage after failure to meet ATP criteria is one of several options; another option is to refine the control strategy, e.g., the routine replication strategy (*10*).

In this example, a tolerance interval approach is used. Before beginning a qualification study, recovery data collected during stage 1 can be assessed using a tolerance interval approach. This assessment is usually done with spiked samples. A method precision study—using the

proposed routine procedure with its controls to test the finished product may also be performed. These studies are intended to provide supporting evidence for the absence of significant bias and a confirmation that the precision is at an appropriate level before qualification of the procedure. Although bias and precision estimates at this stage do not guarantee that a qualification study will be successful, they can flag a potentially problematic procedure.

EXAMPLE USING DATA FROM A RECOVERY STUDY AND A METHOD PRECISION STUDY

Scenario 2 in *Table 1* is used as a guide. The ATP is as follows:

ATP: The procedure must be able to quantify [analyte] in the [describe test article] in the presence of specified impurities and excipients so that the reportable values fall within a TMU of ±3.0%.

The simulated data in *Table 2a* were obtained for the following recovery design:

- Six determinations at 80%
- Six determinations at 120%
- Six determinations at nominal concentration

Simulated data for a method precision study to include six sample preparations of the finished product using the proposed routine procedure and its control strategy thus far are listed in *Table 2b.*

Table 2a. Simulated Data Generated for a Recovery Study

Level	Determinations (%)						Average	%RSD
	1	2	3	4	5	6		
80%	101.4	98.7	100.0	99.7	101.8	100.4	100.3	1.15%
100%	100.3	99.8	98.7	101.6	99.5	99.4	99.9	0.99%
120%	99.3	100.6	101.5	101.3	100.2	98.4	100.2	1.20%

Table 2b. Simulated Data Generated from a Method Precision Study

Sample	Percent of Label Claim (%)						Average	%RSD
	1	2	3	4	5	6		
	101.3	98.9	98.4	101.1	99.7	101.2	100.1	1.27

The average values in *Table 2a* and *Table 2b* indicate that there is negligible systematic error (bias) at all concentrations. Studies performed during stage 1 should support this. The small difference between the target values and 100% is assumed to be due to random error and reflect the real variance in the procedure (this will be investigated further during the qualification study in stage 2). Therefore the bias (systematic error) is considered to be zero. The tolerance intervals can be calculated by entering the following into the tolerance interval calculator at http://statpages.info/tolintvl.html:

- Precision estimates in *Table 2a* and *Table 2b*

- Average: 100.0% (bias is zero)
- Proportion: 90%
- Desired confidence: 50%
- Number of replicates: 6

The TMU of ±3.0% described in the ATP is used as target criteria for the following tolerance intervals shown in *Table 3*:

Table 3. Calculated Tolerance Intervals for Qualification Study Using a TI Calculator

Level	Calculated Tolerance Interval	Meets Target Criteria of ±3%
80%	−2.2 to +2.2	Yes
100%	−1.9 to +1.9	Yes
120%	−2.3 to +2.3	Yes
Method precision study	−2.42 to +2.42	Yes

The calculated TIs at each concentration of the recovery study and the method precision study meet the target criteria of ±3.0% with a 90% proportion and 50% confidence. This indicates that the procedure, when run with its control strategy, is capable of generating results that will meet the requirements of the ATP. At the conclusion of the design stage, a control strategy is proposed and is included with the procedure conditions. The procedure is ready to be qualified.

STAGE 2: PROCEDURE PERFORMANCE QUALIFICATION

Once an ATP has been established, design activities are complete, knowledge is compiled and documented, and a procedure control strategy has been proposed and shown to pass a recovery study, the performance of the procedure is ready to be qualified. The purpose of qualification is to confirm that the procedure meets the ATP criteria and remains appropriate for the testing of the product and the environment in which it is to be used routinely. Qualification consists of a study in which the precision of the reportable value is assessed. The laboratory that will be using the procedure to generate results should perform the qualification study. It is envisioned that this may also replace the current method transfer approach and will include the implementation of compendial procedures. A protocol is drafted and the qualification study is executed by following the procedure as written and with the appropriate controls. Note that the ATP does not specify the details of the experimental protocol to be used to qualify the analytical procedure, although it does provide the primary acceptance criteria for the study.

The qualification experiments are performed according to a protocol and compared against the predetermined acceptance criteria described in the ATP. The protocol should include, but is not limited to, the following: the ATP criteria, proportion, and confidence values for the qualification study (if appropriate to the specific ATP approach); a description of or reference to the procedure including its control strategy; a description of the experiments including the number of standards, test sample, and series analysis that will be performed; and the statistical approach to be used to analyze the data. The system suitability described in a compendial procedure should be considered as a minimum control strategy during the qualification stage. Ideally, the control strategy has been optimized prior to entering the qualification stage. Any additions to the control strategy should be included in the analytical procedure attached to the qualification protocol. Some

examples of these additions may be clarification of laboratory sample preparation instructions, composite strategy (*11*), routine replication strategy (*8*), and addition of environmental controls.

Qualification strategies will depend on the criteria described in the ATP and on the intended use of the procedure. An example of a qualification strategy is provided in this article; however, other approaches and designs are acceptable. Note that some qualification strategies may require consultation with a statistician.

EXAMPLE QUALIFICATION STRATEGY

The ATP used in this example is as follows:

ATP: The procedure must be able to quantify [analyte] in the [describe test article] in the presence of specified impurities and excipients so that the reportable values fall within a TMU of ±3.0%.

This particular qualification design consists of four series with six determinations for each series, where a series is a single run by a given analyst on a single instrument on a given day. This example is based on simulated data considered to be representative of a typical tablet formulation. The data were simulated with the following inputs: True batch mean = 100.0%; within series %RSD = 1.0%; between series standard deviation = 1.0%.

When using a TI approach, the proportion and level of confidence are captured in the protocol prior to starting the qualification study. This example used a proportion of 90% and a confidence of 50%. Note that the design of the qualification study, i.e., the number of series and determinations, has an impact on the reliability of the estimated precision. Consultation with a statistician can be helpful in developing an appropriate design. In this example, a 4 × 6 design is applied.

Table 4. Simulated Data Used to Demonstrate an ATP Qualification Study

Series	Determinations						Average	SD	%RSD
1	100.3	99.9	98.8	101.5	100.1	100.2	100.1	0.8790	0.88%
2	99.2	100.2	100.1	100.7	100.9	101.3	100.4	0.7284	0.73%
3	101.9	99.5	98.6	101.0	98.6	99.8	99.9	1.3178	1.32%
4	101.8	100.6	101.7	102.1	101.3	101.1	101.4	0.5554	0.55%
Calculated TI[a]								−1.9 to +2.8	
Average (n = 24)								100.47	

[a] Calculated TI is discussed in Hoffman and Kringle (*12*).

The total variance of an analytical procedure often is partitioned into components attributable to the different sources of variability. The first source is the observed variation when an analytical procedure is used repeatedly to assess the same sample over a short period of time by a single analyst using the same equipment (where each replication involves the entire process including the sample preparation). This is referred to as the repeatability component.

The second source is variation that occurs when an analytical procedure is used in the same laboratory under random conditions such as different analysts, equipment, or days. The sum of these two components is called intermediate precision (or ruggedness). For the design in *Table 4*, the intermediate precision and TI can be calculated as shown in the *Appendix*. The TI tool used in stage 1 is not appropriate for this type of design because it does not correctly consider the degrees of freedom and sources of error for multiple series.

As shown in *Table 4* the TI calculated for this example is −1.9 to +2.8 (98.1–102.8), which is within the ATP criteria of ±3.0%. The ATP criteria have been met, and the procedure is considered to be qualified for routine use.

At the conclusion of the qualification stage, the study results are documented in comparison to the ATP requirements, and a conclusion is written as to whether the procedure has been shown to meet ATP criteria. If the outcome of the qualification process is satisfactory, the laboratory is considered to be qualified to run the procedure in routine applications.

The calculated TI is for a single reportable value. If the TI for these single reportable values falls outside the established ATP criteria, the procedure can be re-evaluated, including consideration of the following steps:

1. Confirm that the control strategy is optimized for the test environment.
2. Examine the routine replication strategy used to calculate a reportable result, i.e., increase the number of replicates (*9*).
3. Redevelop the procedure (stage 1).
4. Consider implementation of alternative analytical technology (stage 1).
5. Confirm that the probability and confidence values that were selected are appropriate for the intended use of the procedure.

STAGE 3: PROCEDURE PERFORMANCE VERIFICATION

Stage 3 of the procedure lifecycle ensures that the analytical procedure remains in control and continues to meet the ATP criteria. Therefore, the ATP is used as a reference point from which to monitor the performance of the procedure during stage 3 of the lifecycle of the analytical procedure.

The performance of the procedure and its ability to generate results that meet the ATP criteria should be monitored throughout the lifecycle. Routine use of analytical procedures in the testing lab provides the opportunity to trend performance. This is discussed in more detail in the control strategy article (*8*). Note that it may not be practical to trend the TMU described in the ATP. This is because the error is a combination of both the systematic (bias) component and the random (precision) component, and it is difficult to monitor the systematic component under our current industry paradigm. Therefore it is acceptable to trend the precision of the results as well other events, such as system suitability failures and confirmed OOS results.

In some cases it may be necessary to revise the ATP criteria. Changes to the ATP can be triggered by updates to specifications as a result of monograph updates. Changes and the associated rationale should be captured. Any changes to ATP criteria should trigger reassessment of the analytical procedure against the revised ATP criteria.

CONCLUSIONS

This article discusses in greater detail the ATP concept that was discussed in the *Stimuli* article published in 2013, *Lifecycle Management of Analytical Procedures: Method Development, Procedure Performance Qualification, and Procedure Performance Verification* (*13*). It

provides a simple example showing how to establish criteria that can be used to assess the quality of final test results that are used to make decisions about pharmaceutical products. Elements of accuracy and precision from ICH Q2 and ⟨1225⟩ are assessed holistically to show how they contribute to TMU. Although the example shown here focuses on a tablet drug product assay test, the concepts may also be applicable to other types of tests. In addition, statistical approaches other than TIs may be applied as appropriate. The main objective of this article is to provide a simple example showing how sources of variability described in ICH Q2 and ⟨1225⟩ can be considered together to provide a better link between the performance of a procedure and the decisions made with reportable values generated in pharmaceutical analytical laboratories. An additional advantage of using an ATP is that it can drive the development of a robust control strategy, resulting in better, more consistent performance of an analytical procedure throughout its lifecycle.

APPENDIX

Calculation of Intermediate Precision and B-Content TIs for the Qualification Study in Table 4

In *PF* 40(5), the In-Process Revision of *Statistical Tools for Procedure Validation* ⟨1210⟩ gives the following formulas for calculating the mean ($\overline{Y}$) and intermediate precision: $(\hat{\sigma}^2_{ip})$. The mean is calculated by summing (Σ) all determinations across all series and dividing by the total number of determinations:

$$\overline{Y} = \frac{\sum_{i=1}^{r}\sum_{j=1}^{c} Y_{ij}}{cr}$$

The intermediate precision is a function of two variance components, S_1^2 and S_2^2, where $\overline{Y}$ is the mean of the i^{th} series and Y_{ij} is the j^{th} determination in the i^{th} series:

$$S_1^2 = \frac{r\sum_{i=1}^{c}\left(\overline{Y}_i - \overline{Y}\right)^2}{c-1}$$

$$S_2^2 = \frac{\sum_{i=1}^{c}\sum_{j=1}^{r}\left(Y_{ij} - \overline{Y}_i\right)^2}{c(r-1)}$$

$$\overline{Y} = 100.47$$

$$S_1^2 = 2.742$$

$$S_2^2 = 0.834$$

$$\hat{\sigma}^2_{IP} = \left(\frac{1}{r}\right)S_1^2 + \left(1-\frac{1}{r}\right)S_2^2$$

$$\hat{\sigma}^2_{IP} = \left(\frac{1}{6}\right)*2.742 + \left(1-\frac{1}{6}\right)*0.834 = 1.15$$

An upper 100(1–α)% confidence bound U_{GW} for $\hat{\sigma}^2_{IP}$ is based on a method from Graybill and Wang (*14*). This method is called the modified large-sample confidence interval and has been recommended for biopharmaceutical applications by Nijhuis and van den Heuvel (*15*). This formula is:

$$U_{GW} = \hat{\sigma}^2_{IP} + \sqrt{H_1^2\left(\frac{1}{r}\right)^2 (S_1^2)^2 + H_2^2\left(1-\frac{1}{r}\right)^2 (S_2^2)^2}$$

$$U_{GW} = 1.15 + \sqrt{1.47^2\left(\frac{1}{6}\right)^2 7.52 + 0.29^2\left(1-\frac{1}{6}\right)^2 0.696}$$

$$U_{GW} = 1.86$$

$$H_1 = \frac{c-1}{\chi^2_{\alpha;c-1}} - 1$$

$$H_1 = \frac{4-1}{1.21} - 1 = 1.47$$

$$H_2 = \frac{c(r-1)}{\chi^2_{\alpha;c(r-1)}} - 1$$

$$H_2 = \frac{4(6-1)}{15.45} - 1 = 0.294$$

Hoffman and Kringle (*12*) recommend using the B-content TI to assess accuracy and precision simultaneously.

A two-sided B-content TI is:

$$\bar{Y} \pm Z_{\frac{1+\beta}{2}} \sqrt{\left(1+\frac{S_1^2}{rc\hat{\sigma}_{IP}^2}\right)} x U_{GW}$$

$$100.47 \pm 1.645 \sqrt{\left(1+\frac{2.742}{6x4x1.15}\right)} x 1.86$$

where: $\bar{Y}$ = average of all determinations

c = number of series (n = 4)

r = number of determinations per series (n = 6)

$\hat{\sigma}_{IP}^2$ = intermediate precision

S_1^2 = among-run mean sum of squares

S_2^2 = mean squared error

U_{GW} = upper confidence bound

H_1 = ratio of the degrees of freedom for the chi-square to the critical value from the chi-square distribution

H_2 = ratio of the degrees of freedom for the chi-square to the critical value from the chi-square distribution

$\chi_{\alpha;c-1}^2$ = the percentile of a central chi-squared distribution with c= −1 degrees of freedom and area to the left

$Z_{\frac{1+\beta}{2}}$ = represents a standard normal quantile with area $\frac{1+\beta}{2}$ to the left.

REFERENCES

1. Bettencourt da Silva R, Williams A, eds. *Eurachem/CITAC Guide: Setting and Using Target Uncertainty in Chemical Measurement*. First edition. Leoben, Austria: Eurachem; 2015. https://www.eurachem.org/images/stories/Guides/pdf/STMU_2015_EN.pdf. Accessed 29 June 2016.
2. Burgess C, Curry P, LeBlond DJ, Gratzl GS, Kovacs E, Martin GP, et al. Fitness for use: decision rules and target measurement uncertainty. *Pharm Forum*. 2016;42(2).
3. Hubert P, Nguyen-Huu JJ, Boulanger B, Chiap P, Cohen N, Compagnon PA, et al. Harmonization of strategies for the validation of quantitative analytical procedures. A SFSTP proposal--part I. *J Pharm Biomed Anal.* 2004;36(3):579–586.
4. Sondag P, Lebrun P, Rozet E, Boulanger B. Chapter 16: assay validation. In: Zhang L, ed. *Nonclinical Statistics for Pharmaceutical and Biotechnology Industries*. Cham, Switzerland: Springer International Publishing AG; 2016:415–433.
5. Lister AS. Chapter 7: Validation of HPLC methods in pharmaceutical analysis. In: Ahuja S, Dong MW, eds. *Handbook of Pharmaceutical Analysis by HPLC: Separation Science and Technology. Volume 6*. Amsterdam: Elsevier B.V. 2005:191–217.

6. Geetha G, Raju KNG, Kumar BV, Raja MG. Analytical method validation: an updated review. IJAPBC. 2012;1(1):64–71. http://www.ijapbc.com/files/11.pdf. Accessed 29 June 2016.
7. International Council for Harmonisation (ICH) website. ISO/IEC guide 98-3:2008. Uncertainty of measurement--part 3: guide to the expression of uncertainty in measurement (GUM:1995). http://www.iso.org/iso/catalogue_detail.htm?csnumber=50461. Accessed 29 June 2016.
8. Nickerson B, ed. *Sample Preparation of Pharmaceutical Dosage Forms: Challenges and Strategies for Sample Preparation and Extraction*. New York: Springer US; 2011.
9. Kovacs E, Ermer J, McGregor PL, Nethercote P, LoBrutto R, Martin GP. Analytical control strategy. *Pharm Forum*. 2016;42(5).
10. Ermer J, Agut C. Precision of the reportable result. Simultaneous optimisation of number of preparations and injections for sample and reference standard in quantitative liquid chromatography. *J Chromatogr A*. 2014;1353:71–77.
11. Harrington B, Nickerson B, Guo MX, Barber M, Giamalva D, Lee C, et al. Sample preparation composite and replicate strategy for assay of solid oral drug products. *Anal Chem*. 2014;86(24):11930–11936.
12. Hoffman D, Kringle R. A total error approach for the validation of quantitative analytical methods. *Pharm Res*. 2007;24(6):1157–1164.
13. Martin GP, Barnett KL, Burgess C, Curry PD, Ermer J, Gratzl GS, Hammond JP, Hermann J, Kovacs E, LeBlond DJ, LoBrutto R, McCasland-Keller AK, McGregor PL, Nethercote P, Templeton AC, Thomas DP, Weitzel MLJ. Lifecycle management of analytical procedures: method development, procedure performance qualification, and procedure performance verification. *Pharm Forum*. 2013;39(5).
14. Graybill FA, Wang CM. Confidence intervals on nonnegative linear combinations of variances. *J Am Stat Assoc*. 1980;75:869–873.
15. Nijhuis MB, van den Heuvel ER. Closed-form confidence intervals on measures of precision for an interlaboratory study. *J Biopharm Stat.* 2007;17(1):123–142.

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