LIFE CYCLE ASSESSMENT (LCA) APPROACH TO ANALYTICAL METHOD DEVELOPMENT: A REVIEW


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ABSTRACT

Analytical method lifecycle is a continuous process that improves and documents the understanding of the capabilities of each analytical method used throughout the clinical development of a new drug candidate. Of key importance, analytical lifecycle-related activities have to be appropriately staged in accordance with the regulatory requirements without neglecting the financial and time constraints incurred by each project. Currently, regulatory requirements for analytical methods are primarily directed at prerequisites for commercial manufacturing, the end point of the development process, without any description of requirements regarding the stepwise development leading to validation. Results generated using analytical procedures provide the basis for key decisions regarding compliance with regulatory, compendial, and manufacturing limits. The results are applied against Decision Rules that give a prescription for the acceptance or rejection of a product based on the measurement result, its uncertainty, and acceptance criteria, taking into account the acceptable level of the probability of making a wrong decision. The Analytical Target Profile (ATP), risk management, control strategy, and knowledge management are cornerstone concepts in lifecycle management. This article proposes an analytical lifecycle roadmap that will stage the various steps involved in analytical method development while attempting to meet the expectations of the stakeholders involved in the management of project risk, development costs, and regulatory compliance. Application of lifecycle management concepts to analytical procedures provides an opportunity to use the knowledge gained from
the application of scientific approaches and quality risk management to continual improvement and assurance of data quality. Analytical method lifecycle refers to the combined activities of analytical method development, improvement, qualification, validation, transfer, and maintenance related to GMP production. An integrated approach to analytical lifecycle must ensure that analytical methods evolve from initial development to commercial use in a manner that is best suited for their intended use at the various clinical stages on the way to commercialization. Building an analytical lifecycle roadmap that satisfies all requirements must be supported by strong technical expertise as well as sound business and regulatory knowledge.

**KEYWORDS:** Life Cycle Assessment, Analytical Method Development, ATP, Risk Management, Control Strategy, Knowledge Management.

**INTRODUCTION**

Life-cycle assessment (LCA, also known as life-cycle analysis, ecobalance, and cradle-to-grave analysis) is a technique to assess environmental impacts associated with all the stages of a product's life from cradle to grave (i.e., from raw material extraction through materials processing, manufacture, distribution, use, repair and maintenance, and disposal or recycling). LCAs can help avoid a narrow outlook on environmental concerns by: Compiling an inventory of relevant energy and material inputs and environmental releases; Evaluating the potential impacts associated with identified inputs and releases; Interpreting the results to help make a more informed decision.

A life cycle approach identifies both opportunities and risks of a product or technology, all the way from raw materials to disposal. To do this there is a continuum of life cycle approaches from qualitative (life cycle thinking) to comprehensive quantitative approaches (life cycle assessment studies). People, companies and governments use these various life cycle approaches in anything from day to day shopping, selecting office supplies for the workplace, engineering a new product design, or developing a new government policy. A life cycle approach means we recognize how our choices influence what happens at each of these points so we can balance trade-offs and positively impact the economy, the environment, and society. A life cycle approach is a way of thinking which helps us recognize how our selections – such as buying drugs, electricity or a new t-shirt – are one part of a whole system of events.
Analytical methods are at the core of demonstrating the quality of pharmaceutical products. When these methods fail to perform as expected, the quality of these products is called into question. Certainly, we expect to identify quality issues if they exist, but we want to avoid raising the alarm if the issue is only because the method is not performing as expected. Virtually every laboratory has experienced issues resulting from methods that were not sufficiently rugged or well designed, and we propose that these issues may be avoided by implementing a systematic process for method lifecycle that addresses many issues that can be anticipated. This approach is illustrated in Figure 1. Building on the traditional processes of method development, method validation and method transfer, the lifecycle approach incorporates some additional elements including identification of an analytical target profile, use of quality-by-design elements to enhance method understanding, use of an expanded qualification process and introduction of a change control approach to continued method usage. This lifecycle approach can be broken down into three stages: method design, method qualification and continued method verification.

As the demand for new drugs is rising, the pharmaceutical industry faces the quest of shortening development time, and thus, reducing the time to market. Environmental aspects typically still play a minor role within the early phase of process development. Nevertheless, it is highly promising to rethink, redesign, and optimize process strategies as early as possible in active pharmaceutical ingredient (API) process development, rather than later at the stage of already established processes. The study presented herein deals with a holistic life-cycle-based process optimization and intensification of a pharmaceutical analytical method development targeting a low risk, low cost, high performance, prior knowledge, significantly more robust and quality submission to regulatory authorities for faster drug approval (regulatory compliance), scientific expertise.
Analytical Chemistry is the branch of Science that uses advance technologies in determining the composition by analytical technique. We can achieve both qualitative as well as quantitative results. Analytical instruments play a major role in the process to achieve high quality and reliable analytical data. Thus everyone in the analytical laboratory should be concerned about the quality assurance of equipment.

Analytical method could be spectral, chromatographic, electrochemical, hyphenated or miscellaneous. Analytical method development is the process of selecting an accurate assay procedure to determine the composition of a formulation. It is the process of proving that an analytical method is acceptable for use in laboratory to measure the concentration of subsequent samples. Analytical methods should be used within GMP and GLP environments and must be developed using the protocols and acceptance criteria set out in the ICH guidelines Q2(R1). The prerequisite for method development are as follows:[1-4]

1. Qualified and calibrated instruments
2. Documented methods
3. Reliable reference standards
4. Qualified analysts
5. Sample selection and integrity
6. Change control

An analytical procedure is developed to test a defined characteristic of the substance against established acceptance criteria for that characteristic. In the development of a new analytical procedure, the choice of analytical instrumentation and methodology should be based on the intended purpose and scope of the analytical method. The important parameters that may be evaluated during method development are specificity, linearity, limits of detection (LOD) and quantitation limits (LOQ), range, accuracy and precision (Table 1). During early stages of method development, the robustness of methods should be evaluated because this characteristic ultimately helps to decide which method will be approved. Analytical procedures development is primarily based on a combination of mechanistic understanding of the basic methodology and prior experiences. Experimental data from early procedures can be used to guide further development. The ability to provide accurate, reliable and consistent data is the motive of the analytical chemist. Method development procedures are complex, extended and expensive endeavors. An analytical method details the steps and techniques necessary to perform an analysis. This may include: preparation of samples, standards and
reagents; use of apparatus; generation of the calibration curve, use of the formulae for the calculation etc. Analytical Method Development is required for.\textsuperscript{[1-4]}

1. Herbal products and their potency
2. New process and reaction
3. New molecules development
4. Active ingredients (Macro analysis)
5. Residues (Micro analysis)
6. Impurity profiling
7. Component of interest in different proportion
8. Degradation studies.

**Table 1: The parameters of an analytical procedure**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Identification</th>
<th>Impurities Quantitative Limit</th>
<th>Assay</th>
</tr>
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<tbody>
<tr>
<td>Accuracy</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Precision</td>
<td>-</td>
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<tr>
<td>Specificity</td>
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<tr>
<td>Detection limit</td>
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<tr>
<td>Quantitation limit</td>
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<td>-</td>
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<tr>
<td>Linearity</td>
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<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Range</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Robustness</td>
<td>+</td>
<td>+</td>
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</table>

The United States Pharmacopoeial Convention (USP) has been a strong advocate of this process. General chapter *Validation of Compendial Procedures* 1225, which was first published in *USP XXI* (1989), served as the foundation for the development of the ICH Q2 Guidance on Validation of Analytical Procedures (1). More recently, USP has further led on this topic with the publication of general chapters *Verification of Compendial Procedures* 1226 and *Transfer of Analytical Procedures* 1224. (Figure 1).

**Figure 1. Current typical process for analytical procedures.**
The lifecycle concept described in ICH Q8 is adaptable to analytical procedures if we consider an analytical procedure as a process and the output of this process as the reportable result, that is, the value that will be compared to the acceptance criterion. The purpose of applying lifecycle principles to analytical procedures is to holistically align analytical procedure variability with the requirements of the product to be tested and to improve the reliability of the procedure by understanding, reducing, and controlling sources of variability. Enhanced understanding of variables that affect the performance of an analytical procedure provides greater assurance that the quality attributes of the tested product can be reliably assessed. The lifecycle management process provides a framework for defining the criteria for and development of an analytical procedure that meets the acceptance criteria. The procedure then becomes part of a continuous verification cycle to demonstrate that it meets the predefined criteria over the life of the procedure.

Implementation throughout the procedure's lifecycle of a change management process that is based on knowledge gained during the procedure's lifetime ensures that the procedure remains fit for its intended use. Key to the general approach is an understanding of overall variability, including variability arising from the manufacturing process as well as the analytical procedure. A focus of USP has understood the variability of its reference materials, which are part of the total variability that should be understood, controlled and, where possible, reduced.

In this article, we discuss how the modern concept for process validation\(^9, 10\), which is based on a lifecycle model, can be applied to analytical procedures.\(^11–14\) We propose that the traditional approaches to validation, transfer, and verification should be integrated into the analytical procedure lifecycle process rather than being viewed as separate entities.

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

**Stage 1**

The first stage, method design, includes three components: the analytical target profile, method development and method understanding. The purpose of the analytical target profile (ATP) is to address the actual requirements of the method. These requirements and criteria
are not necessarily the same as instrument capability; they should correlate to critical analytical performance characteristics and include meaningful acceptance criteria. They may include some or all of the characteristics described in ICH Q22 or USP General Chapter 3, as well as others that are important for the method or for the laboratory. The ATP attempts to address such questions as: What is the purpose of the method (e.g., to measure a major component or stability indicating)? What are the specificity requirements? What are the accuracy and precision requirements? What are the resource constraints (instrumentation, run time, reagents)? Are there other constraints such as extraction challenges or solution stability? An example of an ATP for a chromatographic stability-indicating method is shown in Figure 2. The second component is method development, for which most labs already have some excellent processes in place. We encourage their continued use, augmented with the guidance from the ATP. Once reasonable conditions for the method have been ascertained, and conformance to the ATP requirements has been established, it is time to enhance method understanding by incorporating some quality-by-design concepts. This includes exploring the method operating conditions and performing a risk assessment for the various method parameters. For chromatographic methods, this should address sample preparation as well as chromatographic conditions.

**Practical Approach to Stage**

Let’s discuss how this might be implemented. We’ll use a content uniformity chromatographic method for a solid oral dosage form (tablet) with two potencies as an example. In establishing the requirements, we consider the characteristics listed in USP General Chapter: accuracy and precision, linearity and range, specificity and limit of detection, and limit of quantitation. There may be other criteria that are important to the laboratory, for instance, the analysis must be able to be performed on equipment that is already in the laboratory, with a minimum time period for solution stability and a maximum run time. Previous experience with similar methods and familiarity with the laboratory data acceptance criteria are very helpful in establishing the acceptance criteria. Accuracy and precision are important characteristics for this method, and we want to set an acceptance criterion that limits the probability that we will generate an out-of-specification result if the tablet is within specification, or generate an acceptable result if the tablet is actually out of specification.
Based on previous experience, if we keep accuracy to a mean of +/- 2.0% and method precision to not more than 2.0 percent, we will accomplish this requirement. This also implies that injection must be tighter than method precision, for which a relative standard deviation (RSD) of not more than 1.0 percent should be acceptable. The range required for this method will be selected such that it will cover both potencies, without need for unnecessary second dilutions. Linearity requirements will be fairly standard, so the acceptance criterion for the correlation coefficient of the least squares regression analysis will be set to not less than 0.99, with an added requirement that the y-intercept of the regression line be not more than 4 percent (to avoid unacceptable bias).

Specificity requirements may be minimal, especially if drug substance impurities and drug product degradation products are controlled in separate methods. In this case, let’s assume there is a significant peak at the void volume, so a requirement will be established that the peak at the void volume and the peak of interest must be well resolved, that is, resolution factor (Rs) is not less than 2.0.

Since this method is not intended to address minor peaks, limit of detection and limit of quantitation are not critical quality attributes, and no requirements are set for this method. For the other requirements identified by this laboratory, the acceptance criteria might include HPLC with UV detector for the equipment; solution stability of at least 48 hours to allow the ability to rerun chromatography if necessary; and run time of not more than six minutes, which would allow same day analysis and interpretation of results, when needed.

Figure 2. Example Analytical Target Profile (ATP) for a Stability-indicating Chromatographic Method
Stage 2
The second stage involves demonstration of the method qualification. First, we need to ensure that the facility, the instruments and the analysts are appropriately qualified. This is analogous to installation qualification for instruments. Next, we need to demonstrate that the method meets the requirements identified in the analytical target profile. This is similar to traditional method validation. Finally, at this point we apply the method to actual manufacturing samples in the facility where they will be produced using the analytical equipment and personnel that will be used to generate data. Once again, the qualification experiments may be dependent on the stage of development.

Also, it is anticipated that existing knowledge and data will be utilized whenever feasible. These qualification experiments provide the framework for future method changes or transfers.

By including a step that ensures that the facility, instruments and analysts are qualified, we ensure that the laboratory is prepared to move forward with the method validation (and, yes, there have been instances where this basic step was skipped and methods have subsequently failed the validation experiments), and we establish the expectations for future laboratories that may need to run this method.

Before proceeding to the traditional experiments that evaluate the characteristics listed in USP, it is valuable to verify that the other requirements (instrumentation, solution stability, run time) established by the laboratory have been met. Since the performance of the method is already well understood (based on the activities in Stage 1), demonstration that the method meets the validation requirements should be straightforward, and for most methods a well-designed experiment can accomplish this in two or three days, based on the solution stability requirements.

Looking next at the real-life situation (actual manufacturing samples, facility, equipment and analysts) is a very valuable addition, challenging the method under realistic conditions of use before releasing it for routine purposes.

Stage 3
The third stage addresses continued method verification. This would include continued use in the original laboratory for an extended period of time, but may also involve method revisions,
transfer to a different laboratory or method verification, in the case of a compendia procedure. As we approach any of these changes, is it appropriate to consider the method lifecycle approach and revisit the earlier stages? Are the requirements identified in the analytical target profile still applicable? Have laboratory investigations, out-of-specification results or changes in expectations indicated the need to revisit the requirements? Most quality control or stability laboratories use some form of control charting to watch for trends. Do the control charts identify a cause for concern? For any changes to the method, or Ready Qualify Launch Information Volume Product Data Lifecycle Design Discover Ideation Initiative Management Design BoM contains Material, Formula, Testing & Regulatory Design BOM Manufacturing BOM Materials Formula Testing Regulatory Global Specification Management (Product Data Record) changes to the laboratory in which the method will be executed, a change control approach is recommended. This includes identifying the nature of the change, the rationale for the change and then assessment of the potential impact of the change. Part of this process will examine the need for revalidation or partial revalidation. The data generated during the initial stages of the method lifecycle can be useful in evaluating whether the quality of the data that will be generated by the method following the changes will meet or exceed the quality prior to the changes. The life cycle of an analytical method is brief as shown in Figure 3. The common steps followed in the method development are as follows.

**Figure 3: The life cycle of an analytical method.**

1. Standard analytes characterization
2. Method requirements
3. Literature search
4. Selecting the method
5. Instrumental setup and preliminary studies
6. Optimization of parameters
7. Documentation of analytical figure
8. Evaluation of the method development with the sample
9. Determination of percent recovery of the sample
10. Demonstration of quantitative sample analysis

THE LIFECYCLE APPROACH

Results generated using analytical procedures provide the basis for key decisions regarding compliance with regulatory, compendial, and manufacturing limits. The results are applied against Decision Rules that give a prescription for the acceptance or rejection of a product based on the measurement result, its uncertainty, and acceptance criteria, taking into account the acceptable level of the probability of making a wrong decision. The adoption of a lifecycle approach to ensure the quality of pharmaceutical products has been extensively discussed during the past several years. The concept of Quality by Design (QbD) is understood as a “systematic approach that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management” (ICH Q8). Application of lifecycle management concepts to analytical procedures provides an opportunity to use the knowledge gained from the application of scientific approaches and quality risk management to continual improvement and assurance of data quality. There should be an effective Quality Management System in place consistent with ICH Q10. The concepts described in ICH Q10 complement current GMPs, thus providing an integrated model for a pharmaceutical or similar quality system. This supports continual improvement across the entire lifecycle of the analytical procedure.

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

Analytical Target Profile (ATP)

The analytical target profile (ATP) is a set of criteria that define what will be measured (e.g. the level of a specified impurity) and the performance criteria to be achieved by the measurement (e.g. accuracy, precision and range), but without specifying the method.
On the basis of ATP, different analytical methods and/or techniques are evaluated in a preliminary investigation to approach the method objective, in general with the purpose of achieving maximum selectivity with adequate efficiency, and improving the reproducibility and repeatability of measurements.\(^{[10]}\)

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

The ATP is based on the understanding of the target measurement uncertainty, which is the maximum uncertainty that the data should have in order to maintain acceptable levels of confidence in data quality. This introduces key performance attributes and changes the way we currently define and evaluate analytical performance characteristics. The ATP serves as a reference point for assessing the fitness of an analytical procedure not only in the development phase but also during all changes within the analytical lifecycle and is not linked to a specific analytical method. It is conceivable that more than one analytical procedure can meet the requirement of an ATP. Any analytical procedure that has been demonstrated to be capable to generate data that conform to the performance requirements established in the ATP would be regarded as acceptable (USP general chapter Elemental Impurities—Procedures 233 and USP Medicines Compendium general chapter Assessing Validation Parameters for Acceptable Procedures 14).

Existing procedures also can be evaluated in terms of their ability to meet an ATP. When using a compendial procedure for the first time, an ATP can be derived from monograph specifications, a performance-based monograph, and any existing knowledge of the product.
In assessing new or existing procedures for their capability to meet an ATP, analysts can use statistical methods for analyzing prospectively designed studies.[18] In the case of existing procedures for which significant historical data are available, statistical procedures for retrospective evaluation of historical data such as stability data, laboratory investigations, check samples/controls, release data, and others are available.[19,20] The level of variability present in the historical data may trigger additional studies that aim to understand and reduce or eliminate sources of variability and improve the data quality to meet ATP. See Figure 4 for some examples.

1. Assay: The procedure must be able to quantify (analyte) in (presence of X,Y,Z) over a range of A% to B% of the nominal concentration with an accuracy and uncertainty so that the reportable result falls within ±C% of the true value with at least a 90% probability determined with 95% confidence.
2. Impurity: The procedure must be able to quantify (impurity) relative to (drug) in the presence of components that are likely to be present in the sample within the range from the reporting threshold to the specification limit. The accuracy and precision of the procedure must be such that the reportable result falls within ±D% of the true value for impurity levels from 0.05% to 0.15% with 80% probability with 90% probability determined with 95% confidence.

Figure 4: Examples of Potential Analytical Target Profiles.

Risk Assessment
A high degree of confidence is needed that the analytical method will generate reportable results that meet the ATP requirements under all conditions of use as the method progresses through the lifecycle. Application of Quality Risk Management (QRM) concepts and tools (ICH Q9) can be valuable in providing a mechanism of achieving this. QRM for analytical procedures can be defined as a systematic process for the assessment, control, communication, and review of risks to the quality of data across the product lifecycle.

There are two risk assessment tools.
1. Failure Mode Effects Analysis (FMEA).
2. Ishikawa Diagrams (Fishbone diagrams).

The variables should include all aspects of the full analytical procedure (Figure 5, i.e., sampling, sample preparation, standards, reagents, facility, and equipment operating conditions. The identified variables then should be evaluated using appropriate risk-assessment tools and prioritized experimentation to understand, eliminate, or mitigate areas
of risk. An approach known as CNX (Control, Noise, and Experimental) can help classify all identified variables. A decision can be made concerning which variables should be controlled (C), which are potential noise factors (N), and which should be examined experimentally (X) to determine acceptable ranges. As part of this exercise analysts should provide and document justifications (prior knowledge, scientific rationale, or others) for the assignments made. Risk-analysis tools can then be used to screen experimental (X) variables for DOE studies to minimize the total number of experiments conducted while maximizing knowledge gained. The results of DOE studies then provide justification of the critical variables and their acceptable ranges (from the risk assessment and experimental work), are inputs in the Analytical Control Strategy, and are explicitly specified in the analytical procedure (Figure 6).

Figure 5: Analytical procedural variables to consider for risk assessment and control strategy.

1. Identify as many variables as possible (prior knowledge)
2. Assign risk based on potential impact on data precision and accuracy (risk identification)
3. The variables identified to have impact on the data will be subject to DOE (risk evaluation)
4. This leads to process understanding
5. Based on the process understanding Risk control
   a. Risk reduction
   b. Risk acceptance
   c. Risk unacceptance
6. Risk review (routine monitoring)
   a. Continuous improvement
   b. Deviation from ATP*

*(Unfavorable trend, potentially result of a change in one or more variables)

Figure 6: Quality risk management, control strategy, and knowledge management: how they work together.
ANALYTICAL CONTROL STRATEGY

A well-developed control strategy, i.e., a planned set of controls, is derived from current product and process understanding. The variables and their acceptable ranges (from the risk assessment or experimental work) should be explicitly specified in the procedure. The controls can include variables and aspects related to the sample, sample preparation, standards, reagents, facility, equipment operating conditions, historical experience (prior knowledge), the format of the reportable value (e.g., number of replicates), and frequency of monitoring and control. The Analytical Control Strategy plays a key role in ensuring that the ATP is realized throughout the lifecycle and also should be considered throughout the lifecycle as part of development, continual improvement, and change management. Different control strategies may be required at different sites. A scientific risk-based approach can be applied to the assessment of a control strategy's suitability across different sites, and quality risk management tools should be used to guide these activities. As an integral part of the laboratory qualification to execute a compendia procedure, the process of quality risk management should be carried out, and the control strategy of the compendia procedure should be verified or expanded in order to ensure that the requirements of the ATP are met. As per analytical point of view CS has been defined as the controls on input factors that ensure the method meets both traditional system-suitability criteria and wider performance-related objectives. System suitability tests are a standard part of routine application and are typically established during method validation. A CS generally includes appropriate system-suitability criteria to manage risks, thus QRA can also help to identify a specific control strategy. An appropriate system-suitability test may be the only control element needed to ensure performance of the selected method, because it helps to identify failure modes and can prevent the generation of erroneous results. An interesting example of CS enabled by a QbD approach was presented by Gavin et al. During robustness studies for an API impurity profile method, they found that resolution of the impurities of interest followed the same trend when method conditions such as n-propanol and temperature were varied. As a result, an early impurity pair was chosen for system suitability and became a convenient method CS, because the two compounds involved were easily obtained. This case is particularly lucky; in general, the system suitability test may need to be augmented with additional controls to properly manage risk. In this sense, a more common strategy could be the definition of accepted ranges for all the critical resolution values. This can be achieved on the basis of the values measured during the system-repeatability study, because system precision provides valuable information about the variability of the analytical system.
KNOWLEDGE MANAGEMENT

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

Figure 7: Summary of proposed analytical procedure lifecycle approach.

We believe that applying a lifecycle approach (Figure 7) to analytical procedures will better ensure that quality objectives are met on a consistent basis.

LIFECYCLE STAGES

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

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

These steps are illustrated in Figure 8 and are discussed in the following text.
STAGE 1—PROCEDURE DESIGN

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

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

The next step is to gain an understanding of how potential sources of variability in the proposed analytical procedure affect the performance characteristics of the procedure. Tools such as process maps and Ishikawa diagrams (fish bones) can be used to provide structure to a brainstorming and information-gathering exercise. Risk-assessment tools (see ICH Q9 for examples) then can be used to identify potential procedural variables that may need to be controlled to ensure procedure performance and to prioritize experimentation to eliminate or mitigate areas of risk. CNX can help classify all the variables. As part of this exercise it is important to provide justifications (for example, prior knowledge or scientific rationale) for the assignments made.

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

Experimental Robustness Studies

Experimental robustness studies address the variations that may occur as the procedure is performed on different occasions. These studies consider both continuous and categorical X (experimental) variables. Continuous variables (e.g., temperature, pH, or flow rate) typically are studied via design of experiments (DoE). For these continuous variables, the output of the DoE study could be a procedure design space within which the procedure performance is ensured. For categorical variables (like column packing batch, type of instrument, etc.) the DoE study attempts to highlight variables that could have a significant effect on procedure performance regarding accuracy and precision, although these variables may have an even
greater effect later in the life cycle. During this study, variables may be identified and may be considered too difficult or expensive to control. These are defined as Noise (N) variables in the CNX scheme. Although N variables are not directly studied at this stage, they are assessed indirectly as part of the Stage 2 activities when a laboratory has to confirm that the analytical control strategy is adequate to allow the procedure to produce reportable results that meet the requirements of the ATP in a particular environment. Example N variables include environmental and routine operating conditions. As a result of the robustness study, a set of operational procedure controls with respect to the C and X variables are defined as part of the Analytical Control Strategy. When uncontrolled categorical variables may result in unacceptable procedure performance, analysts should consider including a check or system suitability test (e.g., chromatographic resolution, symmetry factors, etc.). When such a check is included, it is good practice in the analytical procedure to explain the purpose of the check and the specific categorical variables it is designed to monitor.

Figure 8: Three stages in the proposed lifecycle approach.
Knowledge Gathering and Preparation

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

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

STAGE 2—PROCEDURE PERFORMANCE QUALIFICATION

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

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

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

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

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

**STAGE 3—CONTINUED PROCEDURE PERFORMANCE VERIFICATION**

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

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

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

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

If, during routine monitoring of the procedure, data indicate the procedure is out of control or there is an opportunity or need for improvement, then further action is taken. There are three action triggers (see Figure 9 for examples).

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

Observed Variations

During the investigation, particular attention should be given to special cause variation (shifts, drift, and deviation) and common cause variation (unacceptable noise) (Figure 9). Variation may result when a particular procedure variable is not adequately controlled. This variation may arise for a number of reasons.

- A variable was not identified or adequately studied during the procedure understanding study (Stage 1), and therefore no proper control was defined.
- A variable was not identified or adequately studied during Stage 2 (precision study), and therefore no proper control was defined.
- Series member of a set of categorical variables (not included in the DoE, Stage 1) has been found to have an effect on performance (e.g., a new batch of column packing results in unacceptable performance).
- A control strategy was defined but not followed.
- A noise variable has been found to have an impact on routine performance.
Investigations into inadequate performance should be thorough and well documented and should aim to reach a conclusion about the variable that is truly the root cause. Corrective and preventive action should be taken to ensure the analytical control strategy is updated in the analytical procedure.

**Figure 9: Common variation and special variation.**

**Continual Improvement**
Throughout the procedure's lifecycle, changes may be required to improve the operational performance or the control strategy (continual improvement). Changes may include but are not limited to: inclusion of an additional control, introducing a new method or technology, changing the intended purpose to incorporate a new impurity or tighten specifications, or alignment with a procedure in a compendial monograph that has been updated. The nature of the change dictates the action that should be taken, and a risk assessment should be performed to identify what action is required, and then change should be documented. When the risk assessment identifies a change that requires qualification, the activities described in Stage 2 are performed. This stage also applies to modifications of compendial procedures.\[8\]

Life cycle approach differs from that of the traditional approach of method development. It includes continuous improvement of method performance and the design space allow flexibility for Continuous improvement in analytical method can be done without prior regulatory approval because of design space made previously (Market al., 2010).\[4,9\]

**EXAMPLES OF CHANGES AND APPROPRIATE ACTIONS**

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

**Change Type 2:** These are changes that are outside the already proven ranges but require only confirmation that the procedure continues to generate data that meet ATP requirements. Full procedure redevelopment is not required.
**Change Type 3:** These are changes that involve the need to operate the analytical procedure in a different environment. These types of changes traditionally have been treated as a procedure-transfer exercise (or procedure verification when a pharmacopoeial procedure is used for the first time in a new environment).

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

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

### Analytical Method Lifecycle: A Roadmap for Biopharmaceutical Development

<table>
<thead>
<tr>
<th>Development</th>
<th>Qualification</th>
<th>Validation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regulatory focus</td>
<td>All methods used in process development, characterization and stability testing including raw material testing, in process control, clinical batch release, and analytical characterization (as applicable)</td>
<td>For raw material testing, process validation and commercial batch release, in-process quality decisions, stability testing for commercial shelf-life</td>
</tr>
<tr>
<td>Goal</td>
<td>Establish method, scientific rationale (specificity, stability indication), and laboratory instructions</td>
<td>Confirm method performance and robustness; refine method for better performance and/or higher throughput</td>
</tr>
<tr>
<td>When to</td>
<td>Preclinical stage</td>
<td>Phase I/II</td>
</tr>
<tr>
<td>Where to</td>
<td>Any laboratory</td>
<td>Any lab with sufficient QA oversight</td>
</tr>
<tr>
<td>Sample type</td>
<td>Development batch or surrogate molecule</td>
<td>First representative batch (e.g., tox material)</td>
</tr>
<tr>
<td>Number of batches</td>
<td>One batch (degraded material or stress study)</td>
<td>At least one representative batch (degraded material or stress study)</td>
</tr>
<tr>
<td>Input</td>
<td>Product Critical Quality Attributes</td>
<td>Development data</td>
</tr>
<tr>
<td></td>
<td>Process requirements</td>
<td>Initial system suitability</td>
</tr>
<tr>
<td></td>
<td>Community of Practice</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Literature and prior knowledge</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Output</td>
<td>Method scientific rationale</td>
<td>Readily to validate method</td>
</tr>
<tr>
<td></td>
<td>Analytical procedure</td>
<td>Performance/robustness assessment</td>
</tr>
<tr>
<td></td>
<td>First system suitability</td>
<td>Validation acceptance criteria</td>
</tr>
<tr>
<td></td>
<td>Stability indication</td>
<td>System suitability criteria</td>
</tr>
<tr>
<td></td>
<td>First reference material</td>
<td>Qualified reference material</td>
</tr>
<tr>
<td></td>
<td>Development report</td>
<td>GA-controlled SOP and analysis sheet</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Validated Excel file</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Qualification report</td>
</tr>
<tr>
<td>Failure mode</td>
<td>No failure in development and qualification but method performance capability sufficient for passing the validation</td>
<td>No nonconformity to acceptance criteria and/or validation failure duly investigated</td>
</tr>
</tbody>
</table>

**Fig No 10:** Practical implications of analytical method lifecycle.

**Fig No 11:** The analytical lifecycle roadmap.
COMPARISON BETWEEN TRADITIONAL AND LIFE CYCLE APPROACHES

<table>
<thead>
<tr>
<th>TRADITIONAL APPROACH</th>
<th>LIFECYCLE APPROACH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Validation performed in a check box Manner against ICH Q2 characteristics</td>
<td>Specific ATP produced for each method/application defining the characteristics and criteria that the method needs to meet</td>
</tr>
<tr>
<td>Limited understanding of the impact of variation in method parameters on performance</td>
<td>Detailed structured approach to identifying and exploring method variables</td>
</tr>
<tr>
<td>Method transfer seen as a separate exercise from validation</td>
<td>The activities that are currently performed as part of method transfer are seen as components of the lifecycle approach</td>
</tr>
<tr>
<td>Confusion over the difference between method verification, method transfer and method validation</td>
<td>Improved clarity</td>
</tr>
<tr>
<td>Method validation being a key component of the CMC document</td>
<td>Method qualification documentation being a review issue at inspection</td>
</tr>
<tr>
<td>Separate guidance in USP covering method validation, method verification, system performance verification and transfer of analytical procedure (proposed)</td>
<td>A single guidance on a lifecycle approach to method validation</td>
</tr>
</tbody>
</table>

We all have heard the following so many times in our career: Analytical measurements should be made to satisfy an agreed requirement, Analytical measurements should be made using methods and equipment which have been tested to ensure they are fit for their purposes, Analytical measurements made in one location should be consistent with those elsewhere, Analytical scientists making measurements should be both qualified and competent to undertake the tasks, There should be regular independent assessment of the technical performance of the laboratory and often we also hear about organizations making analytical measurements should have well defined quality control and quality assurance procedures. All these heard lines are true and each one of us work to get around them in a timely fashion but does anyone ever peeped into the heart of an analytical scientist and try to understand the challenges that he/she goes through the lifecycle of their analytical methods that they have developed, validated and successfully transferred to the manufacturing sites. In this article I am making an effort to broaden the understanding of analytical methods and the challenges those methods goes through their entire lifecycle.

The development, validation and transfer of analytical methods are crucial steps in drug development. Analytical testing can provide the data needed to produce safe and effective
drug products. Both the pharmaceutical and biopharmaceutical industries face similar challenges during this process. More challenges typically exist for new types of molecules and/or conjugate products. For example, patient-specific cancer vaccines require conceptually a different approach in that some (routine) test methods should test for non-patient-specific manufacturing (batch-to-batch) consistency versus those that are patient-specific critical quality attributes. A direct potency test method may not exist, and instead, several surrogate test methods may need to be used for potency. Obviously, whenever new test methods are to be used throughout product development, more focus should be on the development, optimization, and validation of these new methods. Often times, the development timelines are compressed for various reasons; however, insufficient consideration is given to analytical method development and validation. People expect the analytical methods to be ready all the time regardless of timeline or resource changes. To handle this challenge, the analytical development team needs to be closely working with the cross-functional development team to anticipate the changes and actively participate in any relevant discussion regarding the timeline. It is also important for analytical development to educate and work with the project managers to be more visible during the development process.

The timing and effort spent on method development correlates with the degree of novelty of the product type and manufacturing process. The sooner methods are developed and optimized; the lower the risk will be to overall product development. Method development and validation are typically done in the product development stage. While the method may go through various iterations during product development, as the final formulation emerges, the method will be optimized and ready for validation. The analytical method will become part of the submission package and, once a submission is approved, there is usually great resistance to submit changes to FDA. So at this point, it is important to have confidence in the method and its ability to be transferred from R&D to quality control or, in some cases, to a contract organization that will be doing the testing. A successful validation will provide this level of confidence. As far as making changes to the method goes, if the changes are necessary, they must be made. Sometimes, changes to a process, necessary reagents no longer being manufactured, improvements in technology or other circumstances out of the lab’s control may result in a method no longer being suitable as written and/or as validated. Depending on the extent of the changes, some form of revalidation is likely to be needed. This may range from a simple verification, demonstrating that the method still performs as intended, to a full-blown validation for significant changes. In addition, this may impact the regulatory
submission; however, the bottom line is if the original method isn’t accomplishing what it needs to accomplish, it needs to be modified and updated to minimize the possibility of inaccurate results. In that event, all appropriate amendments must be made to the original submission.

The International Conference on Harmonization (ICH) has a general guidance on method validation, *ICH Q2 (R1): Validation of Analytical Procedures: Text and Methodology*. This is the guidance that the industry generally follows in performing analytical method validation. The ICH guidance, however, does not specifically address method validation for biopharmaceuticals. Interestingly, FDA issued new draft guidance for industry on *Analytical Procedures and Method Validation for Drugs and Biologics* early this year. The new draft guidance supersedes the 2000 draft guidance for industry on *Analytical Procedures and Methods Validation*, and covers both small-molecule drugs and biologics. In comparison to the 2000 guidance, the new guidance specifically addresses analytical method development and suggests the parameters that should be evaluated during method development, including specificity, linearity, limits of detection (LOD) and quantitation limits (LOQ), range, accuracy, and precision. The robustness of methods is particularly discussed in the new draft guidance, and a systematic approach for method robustness study (e.g., design of experiments) should be adopted to ‘fully understand the effect of changes in method parameters on an analytical procedure’. The new draft guidance refers to the ICH guidance Q2 (R1) for more details on each method validation characteristics and also removes the recommended validation characteristics for various types of tests. For the qualification of new reference standards, the new draft guidance recommends a two-tiered approach, which involves ‘a comparison of each new working reference standard with a primary reference standard so that it is linked to clinical trial material and the current manufacturing process. The new draft guidance does not address specific method validation recommendations for biological and immunochemical assays. I am planning to write a simplified understanding on the new guidance which will be published in the recent times.

During the life cycle of methods we also face several challenges related to method deviations both planned and unplanned. We should distinguish a validation deviation from a validation failure. Both can occur, but the frequency of these events should be low so that the manufacturer can maintain a state of control. In general, an unplanned deviation is typically easier to resolve and may not hold up the completion of the validation study. For example,
the use of an incorrect analyte spike or a confirmed sample mix-up may require an execution repetition but may not need to be treated like a (potential) validation failure once the deviation has been confirmed. Often, a lack of clarity in the validation protocol, poor preparation and planning, and/or insufficient analyst training can result in unplanned deviations. A validation failure results from failing to pass the protocol acceptance criteria (or test method performance specifications). Validation failures are always serious and difficult to deal with under current interpretation of regulatory compliance. PDA TR 57 provides good ideas and suggestions on how to systematically deal with such events and to set up an appropriate quality system, similar to dealing with out-of-specification results.

Analytical method transfers are very challenging exercises and can become more challenging if the receiving laboratories are in different countries/continents. Planning is definitely the key to a successful method transfer. The timelines for method transfer need to be discussed and clearly understood by both the originating and receiving labs. The methods transfer protocols should be carefully reviewed and approved by both labs. Logistics should be well coordinated especially when shipping the reference standards and samples overseas. Proper documentation including import licenses, if necessary, should be obtained in advance. To ensure the success of method transfer, the analytical methods should be evaluated by the receiving laboratory before the initiation of method transfer. The samples for method transfer should also be carefully selected. The new FDA draft guidance recommends that forced degradation samples or samples containing pertinent product-related impurities should be analyzed at both labs for a stability indicating method. For biopharmaceuticals, it might be difficult to ship the forced degradation samples to the receiving lab. A suitable protocol may be needed to guide the receiving labs to generate similar forced degradation samples themselves. When transfers are being done between sites, or with contract facilities, issues may arise with different makes of instruments. While an HPLC has the same basic components, regardless of manufacturer, there may be subtle differences in performance. For example, the construction of the optics in the detector may be just different enough to present unexpected issues with linearity or sensitivity. In some cases, older models from the same manufacturer may have differences in construction that will challenge a method in ways that will prevent a successful transfer. Some exploratory testing may be valuable, prior to transfer, to determine the compatibility of the instruments in the receiving lab and the method.
Method transfer can go smoothly or can result in significant problems. The robustness of the analytical methodology being transferred and the experience of the ‘receiving’ laboratory have a significant impact on the success of the transfer. Differences in instrumentation, culture, and ways of working also contribute to possible challenges, and therefore, need to be considered. The analytical technology transfer (ATT) usually follows an analytical protocol, where results obtained between the ‘receiving’ laboratories are compared to those obtained by the ‘donor’ laboratory transferring the technology. Subjective tests such as color and appearance can cause disproportionate problems unless the specification is carefully worded. Tests with low level impurities require careful evaluation using % absolute differences, rather than student’s t-tests in the ATT protocol. In part, cultural and ‘ways of working’ differences can be overcome through training and short-term secondment, so that analysts in the ‘receiving’ laboratory acquire as much knowledge of the methodology as possible. Like method validation deviations and failures (see ‘Deviations and Variations’), similar root causes may also exist for method transfers (validation extensions). The readiness of the receiving laboratory should be evaluated. Consideration should be given to the availability of required analytical and supporting equipment, software, critical reagents, standards, controls, and analysts who are skilled in the relevant analytical techniques as well as the qualification status of all materials, equipment, and analysts. If gaps are identified (e.g. the receiving laboratory has a similar analytical instrument), a risk assessment should be performed before execution of the formal transfer studies. Shipment and receiving procedures are needed to allow transfer of critical reagents, standards, and samples between laboratories. Incorporation of the test method procedure into the receiving laboratories quality system is also part of the transfer process. The sending laboratory should provide hands-on training in the specific test method to analysts at the receiving laboratory, if needed. The type and amount of training needed will vary depending on the analytical method transferred and the existing experience of the receiving lab and its personnel. The evaluation of the capability of the receiving laboratory to execute the system suitability requirements of the method successfully during the training is recommended. It is important that all responsibilities between sending and receiving laboratories are established. PDA TR 57 provides additional practical tips on what to consider for analytical method transfers. Once the methods are transferred to the respective sites, it becomes a prime responsibility of the site QC/QA departments to monitor them, review and update. Many times the Pharmacopoeial methods (such as USP, EP, BP, JP etc.) are used for testing test specimens in the QC laboratories instead of in-house. The use of these methods needs to be verified against the latest updates of the respective pharmacopeias.
If any changes required as per the updates the methods get updated by using change control forms and brought back in use. The method updating/review part is often raised by the FDA auditors during any inspection.

The Analytical method life cycle is always a challenging process and lots of challenges are invited due to insufficient knowledge and lack of expertise in the area that are required. The drug development is also a continuous process and every year there will be several number of drugs introduced in the market either generic or brand but one common thing that will always remain as is will be the challenging life cycle of all the analytical methods that are/or will be developed for supporting these developmental activities. Following is the flow diagram of analytical method lifecycle.

**CONCLUSION**

Lifecycle management approach to analytical method development and qualification will result in a better understanding and fewer failures of analytical methods due to more robust methods which produce consistent, reliable, quality data throughout the lifecycle. This, in turn, will lead to less method transfer failures, OOS results and method "incidents" when used in the routine environment. A well-developed control strategy, i.e., a planned set of controls, is derived from current product and process understanding. The variables and their acceptable ranges (from the risk assessment or experimental work) should be explicitly specified in the procedure. The controls can include variables and aspects related to the sample, sample preparation, standards, reagents, facility, equipment operating conditions, historical experience (prior knowledge), the format of the reportable value (e.g., number of replicates), and frequency of monitoring and control.
The Analytical Control Strategy plays a key role in ensuring that the ATP is realized throughout the lifecycle and also should be considered throughout the lifecycle as part of development, continual improvement, and change management. Different control strategies may be required at different sites. A scientific risk-based approach can be applied to the assessment of a control strategy's suitability across different sites, and quality risk management tools should be used to guide these activities. As an integral part of the laboratory qualification to execute a compendia procedure, the process of quality risk management should be carried out, and the control strategy of the compendia procedure should be verified or expanded in order to ensure that the requirements of the ATP are met.

REFERENCES


