The inextricable link between product specifications and analytical methods during a product's lifecycle, particularly through clinical and preclinical development, makes intuitive sense: One cannot change significantly without affecting the other; if specifications change for whatever reason their impact on methods must be assessed, and vice versa.

Process development scientists often must change product specifications, or apply methods to an application that was not the original intended use. For example, a method may have originally been developed as a limits test at a specification of \( \geq 4 \text{mg/mL} \), but now a method is required to assess process yields between 90% and 110%. Precision must be significantly higher for quantifying yield, a purpose for which the method had not been assessed. At this point the analytical development group is charged with implementing the required changes as quickly as possible. This exercise becomes more difficult when analytical development is not in direct contact with the processing group, as in the case of a CRO.

This article provides basic background on the nature of product specifications, how they link to analytical methods, and how to maintain that connectivity and communication throughout the product’s lifecycle.

**Key Definitions**

A product specification is a list of tests, references to analytical procedures, and associated acceptance criteria consisting of numerical limits, ranges, or other standards for the tests described. Similarly a critical quality attribute (CQA) is a property demonstrated either through clinical trials, or predicted to be related to the clinical safety or efficacy of the final product.

Each product specification has three key elements:

- **Target quality attribute:** Characteristics confirmed through an identity test, purity test, biological response, or some other analytic approach

- **Analytical test method:** Once a target quality attribute is identified, the method used to test for it.

- **Acceptance criteria:** Attributes that determine whether we accept or reject the batch.
Product Specification Inputs

Justifying product specifications depends on several diverse inputs, including the capabilities of the analytical method, regulations, process capabilities (e.g. variability of the process), characterization and stability studies, data from clinical and non-clinical studies, and knowledge gleaned from the literature on similar molecules.

For example, the World Health Organization stipulates that residual mammalian host cell DNA be present at no more than ten nanograms per dose in finished drug product. Analytical groups must consider this when setting specifications for residual mammalian host cell DNA in the drug substance.

Literature-based knowledge is often sparse or completely absent in early phase 1, meaning that analytical groups must set specifications for molecules for which sparse information is available. Here, experience with molecules within the same class as the development model becomes invaluable.

Perhaps the most consequential factor is analytical method capability: The attribute of interest must be assessable. Thus, the link between methods and specifications are based on the method’s specificity, sensitivity, variability, and accuracy.

Sensitivity and specificity are familiar terms to analytical scientists, and relate to the ability to discriminate between a target analyte and its matrix, unequivocally assess that analyte, and measure it at the required levels.

Related are assay variability (or measurement uncertainty) and accuracy (bias). A product specification of 98% to 102% will not work with an intermediate precision or experimental bias of 10%. Contributions to variability and bias arise from instrumentation (and its proper use and maintenance), sample preparation, the analyst, and the method itself.

Failure to account for the capability of the analytical method when establishing or revising product specifications can result in setting specifications that are unachievable, and ultimately the inability to release product. Analytical groups encountering these problems sometimes attempt to solve them by replicating the experiments, which strains resources, delays projects, and results in cost overruns that might easily have been avoided.

Therefore, continued evaluation of the method throughout the product’s lifecycle is critical for ensuring the link between the analytical method and the associated specification, particularly within a contract testing organization.

Traditionally, the analytical group qualifies the method early in the product lifecycle to assure that it is suitable for its intended use. That qualification usually reduces to a check-box exercise for certifying that the method possesses the appropriate intermediate precision and accuracy.

But a great deal occurs between phase 1 and phase 3: How many analytical scientists can guarantee that the method remains valid when its test article, environment or intended use has changed? The take-home lesson here is always to consider analytical methods when revising or establishing new product specifications.

With the link between methods and associated specifications firmly established, the task becomes maintaining this connection throughout the product’s lifecycle. This may be achieved through Quality by Design (QbD) for analytical method lifecycle management.

The Role of QbD

In recent years, global regulatory bodies have been urging pharmaceutical companies to adopt quality by design (QbD). The International Conference on Harmonisation (ICH) guidance on pharmaceutical development defines QbD as “a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management.” In pharmaceutical manufacturing, QbD refers to quality achieved through process understanding, rather than “testing in” before batch release.

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One may define QbD for analytical methods as the compilation and evaluation of knowledge from the method design stage throughout the method’s lifecycle of use, that establish that a method, when executed appropriately and consistently, delivers quality data.

Applying manufacturing QbD to analytical methods gives rise to three essential elements: analytical target profile, design space, and analytical control strategy.

Analytical target profile establishes the conditions or criteria that need to be met when assessing CQAs. Examples include the ability to evaluate the CQA, the ability to select the target analyte from its matrix, and the precision required to satisfy the requirements of groups downstream of analysis such as process development or manufacturing.

Design space is the multidimensional combination and interaction of input variables and process parameters known to demonstrate quality. When considering design space with regard to analytical methods, one should consider sources and magnitudes of variability, which in turn are associated with the ruggedness of a method with respect to the analyst, instrument, or location, and the method’s robustness.

Control Strategy is a planned set of controls, determined from product and process understanding that ensures process and product quality.

**Figure 1** illustrates the interdependence of the process control strategy, the analytical control strategy, and the product specifications. The information from the process control strategy feeds into the analytical control strategy and product specifications resulting in an environment of continuous improvement during the lifecycle management of the product. Additionally, a constant dialogue is maintained between the process development and analytical groups and the link between specifications and methods is maintained.
QbD for analytical methods can be summarized in four key steps: method performance requirements, method development, risk assessment/analytical design space, and analytical control strategy.

Method performance requirements (or design intent) are based on a fundamental understanding of the criteria the method must meet, the CQAs, and acceptance criteria. This demands that precision and accuracy be a small fraction of the specification, that the method be suitable for target analytes at appropriate concentrations, and usable under routine conditions.

Method development (design selection) is a key decision and requires a clear understanding of the critical quality attributes and the intended use of the method. Moreover the exercise must include a standardized methodology on which manufacturing, processing, and analytical groups agree. Minimizing diversity in method development will drive consistency, and as a result enhance expertise in the method. Total uniformity of methods is not absolutely necessary, but for a given instrument or method platform stakeholders should agree on a standard format through which development occurs, such that the end product looks very similar.

Defining the design space accurately will ensure that the method or methods under consideration will generate accurate, reliable data and meet all performance criteria under all anticipated conditions of use as the method winds its way through its lifecycle. This is a critical component of applying QbD to analytical methods.

Risk assessment tools employed during design space evaluation help to identify where variability in a factor, or failure in part of the system, represent a potential risk to the ability of the method to deliver the design intent. Examples of tools utilized for risk assessment include but are not limited to Fishbone Diagrams, Failure Mode Effect Analysis (FMEA), and Prioritization Matrices.

Successful application of risk assessment results in robustness studies for highest-risk parameters, including design of experiment (DOE) for assessing multidimensional combinations and interactions of the high-risk factors,

Ruggedness studies for the highest-risk system components such as a critical reagent or instrument, and Measurement Systems Analysis (MSA), are used to determine components of variance.

Documented outputs from the robustness, ruggedness, and MSA studies define the design space: Remaining within this space provides a high assurance of consistent results.

The critical parameters and associated acceptable ranges previously identified must be defined during method control (also called control verification). One must also characterize the method system suitability, which encompasses the acceptance criteria that ensure that the method is performing as it should. Some groups also perform instrument checks when applicable, but these are often unnecessary since method suitability should already have provided that information previously.

Finally methods are evaluated to confirm their suitability for intended use. This may take the form of a formal qualification, validation, or verification.

**Method Lifecycle Management**

Applying the principles of QbD to analytical method development, and establishing a control strategy, are merely starting points for the real challenge: managing and updating methods as the process evolves to assure they perform as intended throughout the development and manufacturing lifecycles.
The first step is to monitor method performance continuously through the use of control samples. The methods themselves also need to be evaluated periodically. Under a traditional paradigm the method does not change, nor are potential adjustments considered, between qualification and validation. Analytical groups should instead take advantage of additional information that becomes available, and use it to determine if the method truly is performing at every stage the way it was intended.

How thoroughly this is done should be commensurate with the product development/production phase. Light validation or qualification will usually serve the needs of phase 1 studies while phase 2 demands more involved assessments of data generated between phases 1 and 2. Phase three requires full validation per USP or ICH guidelines.

The robustness of a method should ideally be assessed continuously during method development – not just during the analytical team’s learning curve. Assessment should include performance when parameters – for example column temperature or flow rate in an HPLC analysis – are deliberately adjusted or changed.

Robustness may be assessed during method validation, but that approach is much more difficult than if conducted at strategic junctures times during development. Since validation is essentially a confirmation that the method is working, it is an inappropriate point at which to screen method conditions or gain any additional deep knowledge of performance.

Similarly, evaluating ruggedness should be an ongoing process, for example the types of variability observed between different lots of reagents, columns, or instrumentations, or among analysts. DOE and robustness studies are predicated on previous identification of risk factors and highest-risk modes of failure.

**Summary**

By now the reader should be convinced of the link between analytical methods and product specifications and understand that a method’s capabilities must be considered when establishing or revising those specifications. Utilizing QbD to develop and manage the lifecycles of analytical methods helps to align thinking between manufacturing/process and analytical, which should maintain regular communication throughout development. This assures that the analytical method lifecycle parallels, and supports, the larger product lifecycle.