What Is Test Method Qualification?

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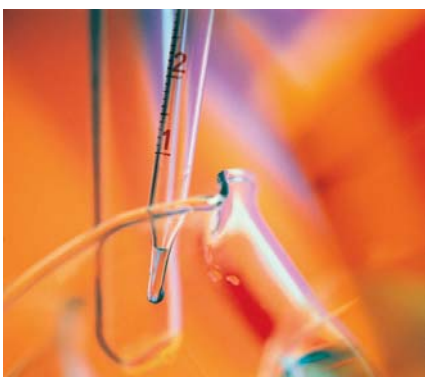
Disclaimer: *It must be noted that the details contained in this manuscript reflect the discussion that occurred during the July 2003 CMC Forum, in addition to the personal experiences of the authors. However, this document does not represent officially sanctioned FDA policy or opinions and should not be used in lieu of published FDA guidances and points to consider or direct discussions with the agency.*

For the purposes of this paper, the words qualified *and* qualification *will be used for simplicity. They are not meant to indicate a consensus endorsement of these terms by the Forum.*

During the development of a biopharmaceutical, a wide variety of analytical technologies are used to assess the physiochemical and functional characteristics of the product. As development proceeds, many of those methods evolve into routine quality control assays that will require validation for their intended use. It is clear that validated test methods are necessary for full compliance with cGMP (**1–3**) and GLP (**4–6**) regulations. Numerous FDA and ICH guidance documents, as well as recent industry publications, give detailed explanations on the elements required in most test method validation studies (**7–18**).

What is less clear are requirements for test methods used during biopharmaceutical development at early stages when complete assay validation may be unnecessary (**19**). Test methods used solely in process validation, or for methods used only for product characterization or comparability studies, may simply be "qualified" for their intended use (**20–21**). For several years there has been considerable debate in the biotechnology community — and at times there have been inconsistent expectations within the agency — regarding the validation status of assays used under such conditions. Even the terminology applied to these test methods is varied: *characterized*, *qualified*, *validated for phase [x]*, or *little "v" validated*. Despite oblique inferences in a few current regulatory documents, no single guidance has yet been published to provide a clear, consistent approach to this issue.



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It is not a trivial distinction to make. There can be significant study management differences between a full cGMP test method validation protocol and the type of protocol used to produce a qualified test method. Depending on the assay technology, a comprehensive method validation study can take three to six months and result in extensive costs (**22**). A less-complex qualification study for the same assay might be completed in less than three weeks at a considerably lower cost. Other opinions on test method validation call for devoting greater experimental time and effort (and therefore cost) on the qualification study than on the validation exercise. In this scenario, method validation consists of a specified number of method confirmation runs in the end-user facility. In some companies, qualification studies (large or small) are reviewed and approved by development scientists, whereas validation studies (large or small) are reviewed and approved by those

PRODUCT FOCUS: ALL BIOLOGICS

PROCESS FOCUS: ANALYTICAL TEST METHOD DEVELOPMENT

WHO SHOULD READ: ANALYTICAL LABORATORY PERSONNEL, R&D, QA/QC, REGULATORY AFFAIRS

KEYWORDS: CHARACTERIZATION, COMPARABILITY, VALIDATION, QUALIFICATION, TEST METHODS

LEVEL: INTERMEDIATE

individuals as well as representatives from the QC and QA departments. Despite differences in the scope of experimental work, documentation formats, and review/approval practices, the prime objective of these studies is to demonstrate adequate capability of the test method to meet appropriate standards of performance for its purpose.

The CMC Strategy Forum on Test Method Qualification

The third Well-Characterized Biotechnology Pharmaceutical (WCBP) Chemistry, Manufacturing and Controls (CMC) Strategy Forum was held on 24 July 2003 on the campus of the National Institutes of Standards and Technologies (NIST) in Gaithersburg, MD, to discuss these issues related to test method qualification. As with the first two CMC Strategy Forums (**23–24**), the California Separation Sciences Society sponsored the event (CaSSS; www.casss.org). More than 90 attendees represented large and small biopharmaceutical companies, government agencies, industry consultants, and academic organizations.

The objective of this forum was to review a wide variety of biotechnology industry practices and discuss possible regulatory expectations for test method qualification versus validation. The goal was to determine whether common elements among the strategies typically used could provide at least a minimal set of benchmarks to reference when conducting or reviewing test method qualification protocols. The first part of the forum consisted of overview comments from senior CBER and CDER representatives regarding current regulatory guidelines related to test method validation and considerations for different method applications. Following the FDA presentations, examples presented by speakers from Amgen, Merck, and an independent pharmaceutical consultant pointed to elements they have found crucial to the successful design and implementation of qualified test methods. The attendees then received a set of four questions to facilitate open discussions for the remainder of the forum (see the "Questions" box).

Questions Posed at the CMC Forum

Question: Does your company conduct a method performance assessment study before (or instead of, for some methods) full ICH validation?

Answers: *Attendees unanimously asserted that they do a study of this nature.*

Question: What do you call this type of study?

Answers: *Highly varied; qualification, verification, characterization, little "v" validation, validation for phase "x", among others*

Question: What do you do in this type of study that is different from complete FDA or ICH assay validation?

Answers: *Widely varying strategies, but many common elements (see article text).*

Question: What is the expected outcome of this study?

Answers: *Varied; assay optimization, assessment of initial method performance specifications, establishment of system suitability and validity criteria, generation of a formal designation for the status of the method (e.g., to formally declare it qualified or characterized), training exercise, technology transfer study, or combinations of these*

Regulatory Considerations for Test Method Validations

Several existing FDA and ICH guidance documents describe the principles of assay validation and when to apply them fully. Some of those documents also suggest when full test method validation may not be required:

Phase 1 IND (19): "Validation [of specific methods] and established specifications ordinarily do not need to be submitted at the initial stage of drug development."

Process validation (20): "It is important that the test methodology be qualified to assure that the test results are objective and accurate."

Comparability Protocols (21): "In some instances, analytical procedures are used in the characterization and/or assessment of the functionality of a product, but not for batch release or for process control (e.g., NMR spectroscopy, carbohydrate structural analysis, attachment site determination). If you specify these analytical procedures in a comparability protocol, we recommend that you provide any replacement or modification to those procedures submitted in the approved application and, as appropriate, report to us results from qualification studies when a post approval CMC change is implemented using the approved comparability protocol."

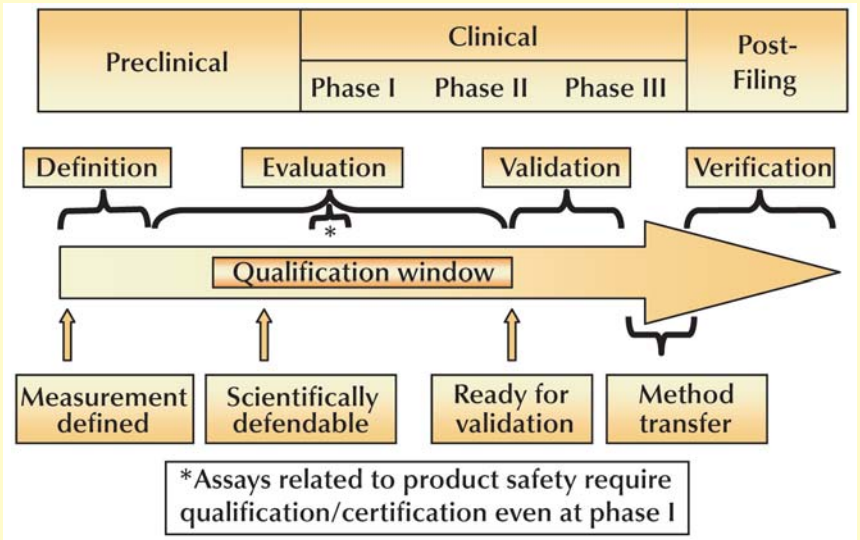
Regardless of the final validation study, FDA expects analytical methods used in product development CMC activities to be sufficient to

- assure the safety of the product
- assure that analytical information gained in development can be reliably related to commercial manufacturing
- provide a sufficient foundation for method validation when appropriate during development or by the time of submission of the product's marketing application.

When Is Test Method Validation Required?

To meet these expectations, and when it is feasible and appropriate, companies should follow the recommendations for the full validation of an assay. The "Regulatory Considerations" box illustrates when "completely" validated assays are required by regulations or recommended by guidance and when assays might not be fully validated. These

Figure 1: Possible timing for assay qualifications that lead to validation



Regulatory Considerations for Test Method Validation

Where "complete" assay validation is required:

- Lot release assays
- Raw material, in process, and excipient testing
- Stability methods for defining expiration dates/holding times
- GLP study assays
- Clinical study assays? (Immunogenicity?)

When the extent of assay validation is dependent on other factors:

- Assays for quality assessment
- Stability methods for defining expiration dates/holding times up to marketing application submission
- Comparability and characterization assays
- Clinical study assays? (phase dependent? biomarkers, immunogenicity?)

requirements or recommendations clearly depend on several factors, including the stage of product development and the intended use of the assay. There is no single algorithm, because some assays, especially those used for GLP animal toxicology or related safety studies, are expected to be validated, despite such studies occurring very early on in the drug development process. For example, process development assays used to assess viral clearance or viral inactivation procedures require validation before their use with phase 1 clinical materials if following GLP as recommended (**25**).

Determining what assays can assess safety is not always straightforward because some product assays (e.g., identity and purity) can detect changes that could potentially affect product safety. Typically, greater confidence is needed for assays that directly assess known safety attributes such as product QC microbial methods (e.g., sterility or bioburden). Such assays often follow official compendial procedures (the *US Pharmacopeia*, for example), and when followed as written in a user laboratory, they do not require performance of complete validation. It must be noted that the suitability of these methods, as with any compendial method, has to be determined under actual conditions of use (e.g., interference from the test article in a sterility test method) (**7**).

It must also be considered that some assays used for GLP or early safety studies may not be amenable to validation to the extent expected for assays at licensure. Assays used to characterize a product at the preclinical stage (e.g., potency assays) are unlikely to be completely developed or optimized, so a rational, scientifically based approach seems most sensible for such assays at an early stage of development.

Although not a focus of this meeting on assays to address product quality, it was illustrated that assays to support clinical studies, especially those that support safety (e.g., immunogenicity) are generally expected to be fully validated. Clinical laboratories have to be compliant with clinical assay requirements produced by bodies such as CLIA (**26**) and NCCLS (**27**).

Forum participants generally agreed that the typical window for using qualified methods occurs early in the development cycle, as Figure 1 shows. Typically, methods are validated during phase 3 studies in preparation for conducting conforming validation studies and for submitting a marketing application. Validation of critical assays (e.g., potency) may be required before phase 3 to assure the quality of biologics used in those pivotal studies and to provide a stronger link of critical quality parameters to the safety and efficacy of the products.

When it is unnecessary to have a (fully) validated method, at a minimum the assay must be scientifically sound, generally suitable for its intended purpose and stage of product development, and capable of generating reliable results. These are similar to many but not all of the goals for completely validated assays. The difference largely rests in the ongoing confidence in the results and therefore in the amount of operational robustness needed in the validation. When assessing assays during development, regulators look at several factors that influence the amount of validation required. These include factors such as assay complexity, criticality, intended purpose (e.g., safety assessment or characterization, release), and stage of development.

What Distinguishes Qualification from Validation?

A key question posed by this CMC Strategy Forum was, "How do your qualified and validated methods differ from one another?" Although the specific details varied greatly, many common elements emerged from the discussions:

For Qualification of a Test Method:

- There are no predetermined method performance specifications; however, there may be minimal method performance capability requirements based on an intended application.
- Qualification studies are used to determine method performance capabilities for parameters such as specificity, linearity, accuracy, and precision as required for an intended application.
- A method cannot fail qualification; it can (and should) be reoptimized until it can achieve acceptable performance.
- If it cannot achieve the required performance, it should be rejected for the application.

For Validation of a Test Method:

- Method performance specifications should be established before validation begins; validation should not be a discovery or optimization study.
- Specifications must be met by every validation trial run for the validation study to pass.
- A method can fail validation; if it does, assignable cause for the failure should be investigated and resolved before the method can be considered fully validated.

In contrast with qualification, it was generally agreed that validation studies are more rigid method assessment exercises. Some participants indicated that validations should not be a time for analytical discovery; they should be a confirmation of (by then) demonstrated, predictable assay capabilities. Performance expectations are presented as predetermined validation specifications. As such, validation experiments are all "on the record"; that is, if a validation run does not pass established specifications, it can fail the validation study unless a clear assignable cause (e.g. analyst error) can be found and corrected. The rationale for failing a validation study if methods cannot meet predetermined specifications is simple: If the method cannot reliably pass the validation study, what confidence is there that it would perform reliably under routine QC conditions?

Table 1: Matrix example for qualification activities; (X) = typically included; others may be needed in some cases

Requirements	Qualify New Analyst Training	Qualify New Lab Transfer	Qualify Method (New) Qualification	Qualify Method (Commercial) Validation	Qualify Compendial Method (New Sample Type) Verification
System suitability Assay acceptance	X	X	X	X	X
Specificity/ carryover			X	X	X
Linearity/ range			X	X	
Precision		X	X	X	X
Accuracy/ recovery		(X)	(X)	X	
LOD/LOQ		(X)	(X)	(X)	
Standards/samples stability			X	X	X
Robustness				X	
Equivalence comparability of results	X	X	X		

To provide clear guidance to assay developers and end-users, some companies use a "matrix approach" to distinguish among applications and requirements of method qualification and method validation (Table 1). The first column lists parameters to be examined, and the remaining column headers list the applications. Each point where a parameter is required to support the specified application of the method is marked with an "X". The matrix is used to organize several strategies into a consistent, comprehensive approach that is customized for each intended application. It accounts for the major functions of an analytical testing laboratory and provides a clear plan for each method.

Issues Relating to Test-Method Qualification

Forum participants also identified several experimental issues frequently addressed in qualification protocols. Although some of the terms used below are not identical to those in the ICH or FDA method validation guidance documents, the general issues many forum attendees typically addressed in designing qualification study protocols are specificity, "relative" accuracy, sensitivity, "proportionality" or limited linearity, precision, and system suitability.

***Specificity* (can I detect my molecule in its matrix?):** It was noted that experimental confirmation of assay specificity is the first study some conduct when assessing new analytical methods. It prevents an unpleasant surprise later if the method fails to distinguish the analyte from other components present in the sample, rendering the assay completely unsuitable for the intended use. However, in some instances specificity is not a critical assay parameter because it is supported by other, orthogonal analytical methods in the analysis of the product.

***"Relative" accuracy* (can I measure the abundance of my molecule relative to some reference point?):** It was noted that absolute accuracy might be impossible for early-stage applications because an empirically quantitated product reference standard is typically required to get true accuracy. Such a standard often is unavailable until later in development.

Although it may be impossible to obtain absolute quantitation of the molecule or its impurities during early development steps, the capability of a method to distinguish defined changes in the amount of such substances should be demonstrated at least over the initial expected operating range.

***"Proportionality" or limited linearity* (is the signal proportional to the abundance of my molecule over a least a minimal range, even if the method is not strictly quantitative?):** It was noted that full linearity and limit of detection/limit of quantitation (LOD/LOQ) might be unnecessary in early-stage applications unless the intended use of an assay is to quantitate low-level moieties (e.g., if the drug substance and the drug product concentrations are significantly different). It was also noted that the qualification or validation of LOD/LOQ for low-level impurities and degradants might have to be reiterated many times as the process developers generate changes in the product.

***Precision* (do I get the same result if I run this method twice or more using the same sample?):** It was noted that although assay precision based on repetitive testing of one sample does provide a good indication of intra-assay variability, 10 runs of one product lot might provide no more confidence of assay suitability than would three runs of three lots. In addition, the requirements for precision testing of a qualified assay should be based on the needs for the assay. If an assay is going to be optimized over time and not used extensively during that time, then it seems logical that there is less need for considerable precision testing. Reliance on quality control samples and other system suitability measures (see below) is a more useful approach at this stage.

***System suitability* (how can I ensure that my assay system is working when I perform a run?):** It was noted that establishment and routine use of meaningful system suitability measures appropriate to the sample type and analytical technology of a method is one of the most critical tasks of assay development. Because of its value in assessing method performance, it should be done as soon as possible in the product development cycle. Some forum participants noted that evaluating and establishing meaningful system suitability measures — which some maintain are necessary before initiating method validation studies — are among the most critical outcomes of a test method qualification study.

The Scientific Integrity of Test Methods

Whether it is qualified or validated, all forum participants agreed that the scientific integrity of a method is paramount. To focus a method development process, it is important to consider the following questions when selecting and developing any analytical assay. Scientifically-sound approaches to questions such as these should yield an analytical procedure that does what it is intended to do, generates adequate data for its application, and provides confidence in the results. These are principles that good analytical scientists — whether in industry or in regulatory agencies — seek to have confirmed in test method development records, including qualification and/or validation studies.

Q.1 What is the objective of the assay? Several attendees knew of instances in which the objective of an assay was never actually established, or was incorrect, resulting in a misdirected attempt at qualification or validation. A study protocol should state the objective of the assay and specify how the study design will ensure that the objective of the assay is met.

Q.2 What are the appropriate performance characteristics to address? A common mistake is to select parameters for qualification or validation that are not meaningful or to miss potentially critical ones such as reagent variability. Such a mistake seems to happen particularly often with biomolecular methods, which do not necessarily fit chromatographic validation strategies. They frequently require inherently variable, complex reagents and materials. The need for assessment of critical assay materials during assay development and qualification is an important process and often takes the form of robustness testing.

Q.3 Is the performance of the assay acceptable for its application? When the requirements of the product specifications are not factored into the choice or optimization of test methods, participants agreed that "hindsight is 20/20." The inevitable outcome of such a serious omission is to realize (too often, during validation) that the assay as-is will never be capable of meeting the performance characteristics required for its intended use or that its performance-acceptability criteria will require substantial revision for the assay to be used as-is. Acceptable performance criteria for any assay should be developed in association with the "customer" — be it process development, manufacturing, regulatory, or clinical — to try to avoid encountering such issues too late in the process.

Q.4 Do I have sufficient confidence in results obtained from this assay? This question formed the central premise of discussions on using a qualified assay in designated circumstances. What elements are necessary to provide sufficient evidence that a test method will perform reliably under the expected conditions of use? Is a "full" validation study — as defined by current FDA and ICH guidance — the only exercise that can provide adequate experimental proof of suitable assay performance?

Or, as some forum attendees proposed, can an intended use be

better defined to allow a "partial"' validation to establish method performance capabilities within specified limits? For example, if a method's intended use is specified as "RP-HPLC Assay to Determine the Purity of Product X; for Use During Phase 1 Clinical Trials," the QC use of this assay must be limited to phase 1 clinical material, not for all future lots of the product. Assuring suitability for ongoing QC testing would entail numerous robustness experiments under a wide variety of potential operating conditions. But by limiting the validated application to a defined developmental phase, minimal robustness testing of the highest risk operating variables present at that time might adequately show that the method is capable of meeting its restricted intended use. To many, this approach meets the "fit for use"' definition of validation and avoids the use of the confusing term "qualification."

Q.5 How will I objectively demonstrate that each assay I run is valid? Whether a method is to be qualified or validated, forum participants generally considered that including assay controls (or test system suitability measures) is critical for verifying that meaningful results are obtained with each run of the method. In fact, many believed that until, or unless, a method is fully validated, system suitability criteria serve as the greatest source of confidence in its reliable valid performance.

Possible Schemes for Method Qualification and Validation

The forum attendees presented many different strategies to demonstrate their interpretation of relationships between method qualification and method validation studies. Benefits and risks are associated with every strategy. It was acknowledged that ultimately the choice is based on the amount of risk that can be managed for the use of the method. That risk may be mitigated by factors such as demonstrated historical experience with the technology or by stipulating a restricted use of the method. Each organization must define the scenario that best reflects its capabilities and then evaluate its ability to implement it consistently.

Forum participants recognized that test method information evolves during a product development cycle — and beyond. As shown in Figure 2, the increasing stringency of method requirements funnels performance expectations for the method at each phase. Each step forward asks more of a method until all performance requirements are satisfied for its intended use. Regardless of where the qualification-validation line is drawn in this continuum, the data collected at each step build upon the previous set of data. This is the logical scientific progression of method development activities. The result is a comprehensive method development history that (ideally) is captured in a well-documented technical report.

Figure 2: Evolution of method performance expectations

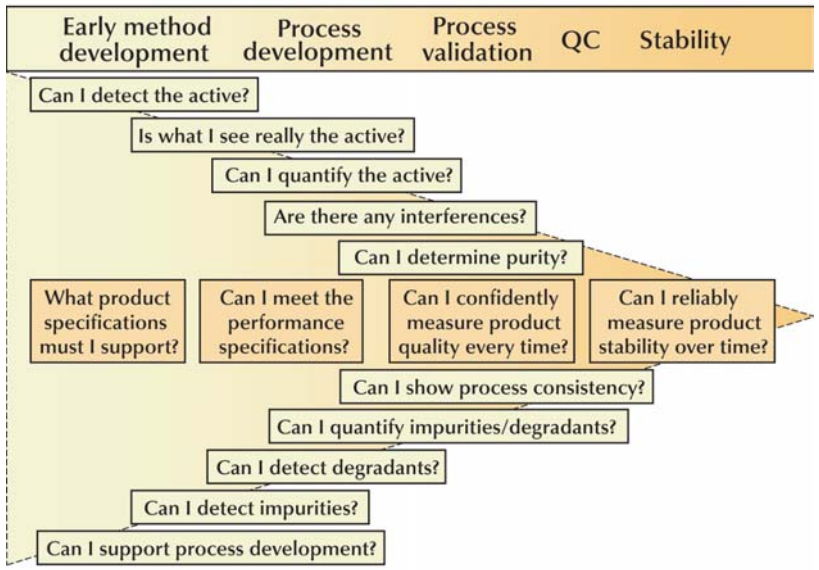
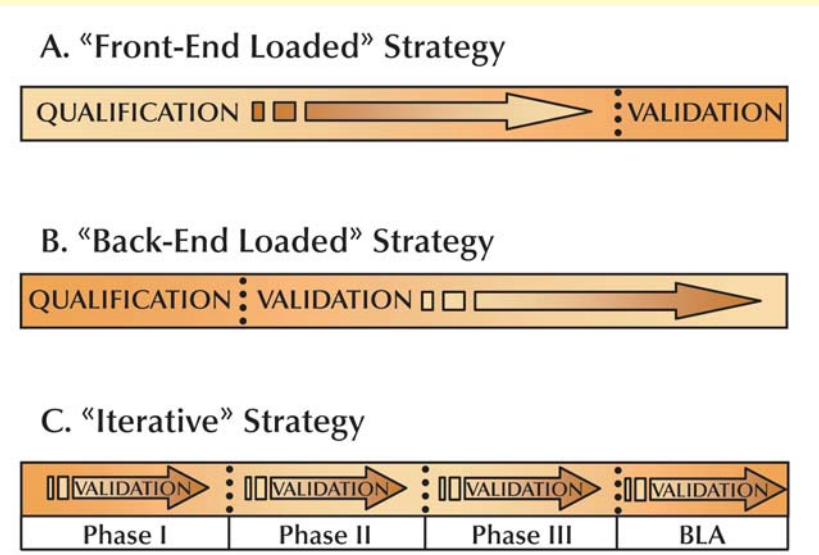


Figure 3: Qualification/validation design strategies during development



Different Qualification Strategies

One concept that varied widely among forum attendees was the division of experimental activities between qualification and validation. Figure 3 illustrates three simple models reflecting the range of views discussed. Several participants commented that whatever term is used to describe method performance studies should be defined internally within an organization and used consistently; the study protocol should include appropriate experimentation to achieve the objective of the study; and adequate documentation should be generated to clearly demonstrate both of those points.

"Front-End Loaded": A "Front-End Loaded" strategy (Figure 3A) places most of the experimentation in the qualification stage, where method capabilities – including robustness and ruggedness — are explored. In this strategy, validation becomes a relatively brief confirmation of method performance in an end-user laboratory. The assay is used in the "qualified" state as the manufacturing process is finalized during product development. When the process is ready for validation, the methods are validated. By that point, there may be a few years of experience using the qualified method with the product. Several participants discussed the value of this approach in terms of minimizing the risks of assay performance surprises when the method is finally validated.

"Back-End Loaded": A "Back-End Loaded" strategy (Figure 3B) reverses this distribution of activities. The qualification is a relatively short study to investigate assay performance parameters such as accuracy, precision, specificity, sensitivity, linearity, and range. The validation study incorporates the robustness and ruggedness elements necessary to determine the variability of method performance under different operational conditions. This approach to qualification was also used by some forum participants for methods restricted to applications that would never require full validation, such as methods used only in characterization and comparability studies. In those situations, the qualified methods would be routinely used, but they would be limited to designated non-QC applications.

"Iterative": A third approach used by some participants was an "iterative" strategy (Figure 3C). In this model, "validation" is the term used for all method performance studies, but it is specifically identified by each intended application. For example, the objective of the study would be linked to use of the method at phase 1, 2 or 3 — such as in "Validation for Phase 1 Applications." At each successive phase, the validation study would be amended to include additional parameters and data required to support the next stage. In practice, experiments conducted are generally the same as those for qualification studies, with increasing levels of robustness and ruggedness collated at each phase.

The rationale for applying the term "validated" in this model is based on the principle that assay validation can be defined by the study protocol, in which the extent of validation is described and scientifically justified. For example, the protocol should address the following types of questions:

- Is specificity required?
- How much precision testing is needed?
- Is reproducibility necessary if only one laboratory will ever carry out the method?

Using this strategy, if the method performance criteria are shown to be acceptable for the assay as intended for its use, has the assay not been "validated" regardless of whether all the criteria described in guidance documents for methods validation have been tested?

Advocates of this strategy point out that it obviates the need for any term other than "validation." It also assures that all methods are validated for their intended use as defined by both the product attribute (e.g., identity or purity) and the stage of product development. Similarly, the methods used only in characterization, comparability, or process validation are "validated" solely for those intended purposes.

Operational Control Elements for Using Qualified Methods

When using qualified test methods, most forum participants shared the view that additional control elements were necessary to assure the integrity of the assay with each run (see the "Recommended Control Elements" box). The first is the preparation and use of an SOP that describes the details of performing each step of a method. If a method is qualified for a specific, limited application (e.g. characterization only), the SOP should include a statement of the restricted scope to assure that the assay is not misapplied in practice. The method SOP should be subjected to change control to assure that all changes are documented and justified because if the data generated with the qualified method are to be used to establish performance specifications, it will be important to know whether the method was conducted the same way each time. If it was not, the differences should be evaluated to ascertain any impact they may have had on the data. Depending on the method changes, it is possible that data collected with earlier versions of the method SOP should be omitted from the historical performance evaluation. To include them could yield a performance specification range that is not reflective of a modified assay's new capabilities.

If a qualified method is intended for use with specified applications, in some cases it may be desirable to also specify the minimum level of training or experience required to conduct the assay. Fully validating an assay for robustness and ruggedness under all expected operational conditions in a user laboratory should account for the

degree of difference inherent in the experiences of the analysts who will be assigned to run the assay. Until (or unless) the assay is fully validated, it may be necessary to restrict the testing assignments to analysts who are more experienced with the assay's technology. This approach might be suitable for techniques that unavoidably involve subjective adjustments to achieve meaningful results or require in-depth data analysis with the consideration of the effects of multiple variables. Such methods are often used in the extended characterization of biotechnology products, and based on the technology, may not be suitable for full validation or routine QC applications.

Regardless of the technology, forum attendees recommended that calibrated instrumentation and performance-qualified equipment should be used in developing and conducting qualified test methods. Although the level of quality practices followed by R&D does not have to approach cGMP standards, development laboratories should attain a minimum level of quality to assure the consistent integrity of their operations (**28**). Most participants acknowledged that good quality practices in development laboratories often have a significant impact on the success of method development projects.

The establishment and use of appropriate system suitability measures were considered by some to serve as qualified method "insurance policies." Without a complete assessment of a wide range of potential variables that could affect the performance of the assay (especially reagents and materials used in the method), internal control measures can signal hidden problems that are independent of the samples being tested. Even when methods are fully validated, system suitability measures can provide some degree of protection if unexpected variations are encountered (**29**).

In cases where a qualified method is ultimately intended for validation against predetermined specifications, many participants indicated that they track and trend the performance of that qualified assay with each use. From these data, method robustness and ruggedness capabilities can be assessed. Even if the runs may all have been in an R&D environment, chances are good that different reagent lots have been used over time, and multiple samples from several production runs will have been tested. For the purpose of assessing method reliability, it is important not to overlook instances in which a qualified assay did not perform as expected. Any such "failure" of a method should be examined carefully to determine whether, in retrospect, an assignable cause could be found. If not, it should be considered whether the "failure" is really an outlier or whether it is a bellwether of inherent assay variability that should not be ignored when establishing performance specifications for method validation.

Internal Policies and Practices: Be Consistent

Finally, participants recommended that organizations provide clear and consistent internal guidance on their preferred strategies and practices for test-method qualification and/or validation. By now, most biotechnology companies have well-established validation policies and SOPs for their implementation. Similar documents should be in place to define and describe the expected activities for test-method qualification, including which organizational entities have review and approval responsibilities for the protocols and reports. In some companies, QA reviews and approves only the final validation activities; in others, technically qualified QA reviewers participate in the review of method development and qualification reports, if not in the prospective R&D study protocols. Regardless of the system used, it should be consistently applied and sufficient to assure that the right studies are done at the right time and that their documentation can be retrieved for review in the future.

A Common Objective

Because of the technical nuances inherent in many analytical methods used with biotechnology products, determining an appropriate test-method qualification or validation strategy requires careful consideration of the nature of the technology and its intended application, as well as of the specific complexities of the product. In the draft FDA Draft Guidance on Analytical Procedures and Method Validation (**7**), validation is described as: " the process of demonstrating that analytical procedures are suitable for their intended use." Elements of risk

Recommended Control Elements for Using Qualified Test Methods

- There must be a written SOP for the test method that is subject to typical document change control systems.
- The method should be approved for use only in limited applications (e.g., characterization, comparability, early phase development, technology transfers).
- The method could be restricted to use by those with a greater level of training (e.g., senior analytical scientists) until or unless it becomes fully validated.
- Each run of the method should use calibrated/qualified instrumentation.
- Each run of the method should include appropriate system suitability criteria.
- Assay performance may be tracked, including method failures, to determine the preliminary robustness of the assay for future specifications.
- There should be a company policy/SOP on qualification studies similar to the company policy/SOP on validation studies.

Risk Assessment Considerations for Analytical Test Methods

- Manufacturers and regulators both want to have confidence in the results from analytical tests regardless of where they are used in the product lifecycle, how they are applied in the manufacturing process, or what purposes they serve (e.g., product release, process control, material evaluation, validation, deviation investigations, comparability assessment). Not fully validating a procedure does not excuse the manufacturer from assuring confidence in the test results.
- Validating an analytical test method is the process of demonstrating that the procedure is suitable for its intended purpose. Within the product development continuum, sufficient information appropriate for the intended use, stage of development, method complexity, and other factors should be accumulated (and appropriately documented) to assure confidence in the test results.
- Complete validation for all analytical procedures used in manufacturing is not necessarily a regulatory expectation or requirement (for some analytical procedures, full validation may be held until submission of a marketing application). However, there is a risk in not completely validating analytical procedures, especially those used in the manufacture and assessment of product for use in pivotal studies. That risk is variable, but manufacturers need to assess and understand the risk and its potential impact.
- A comprehensive, well-written validation report is important in summarizing and communicating the knowledge and understanding, including seminal experimental data, learned from validating the analytical procedure. Such a report provides a needed resource for manufacturers — especially in the changing business and accelerated product development environments — and for regulators with evolving regulatory paradigms.

assessment should be applied in the design of internal policies for the adequate qualification, validation, and documentation of analytical procedures (see the "Risk Assessment" box).

Several steps in the process of developing and validating a test method may involve years of work and dozens of individuals. The outcome of this CMC Strategy Forum demonstrated that there is a great deal of consistency in the nature of the steps for biological and biotechnology products. Although individual strategies can substantially differ on how and when to assure an assay's suitability for use, there was no disagreement among participants that the goal is reliable method performance under the expected conditions of its use.

Acknowledgments

This article is based on presentations and discussions held at the Third CMC Strategy Forum held 24 July 2003 on the campus of the National Institute of Standards and Technologies (NIST) in Gaithersburg, MD. Over 90 industry and government representatives attended this forum. We would like to thank all of the forum attendees for their valuable contributions to the interactive discussions. We would also like to thank everyone who provided additional comments on the draft of this paper.

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