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Validation "PQ Forum" Review—Applications to Quality and Compliance

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PQ Forum Review

ABSTRACT

In partnership with the *Journal of Validation Technology*, the *Journal of GXP Compliance* is pleased to present this "PQ Forum" review. “PQ Forum” is an ongoing feature in the *Journal of Validation Technology (JVT)* that provides a forum for validation practitioners to share information about Validation Stage 2 Process Qualification (PQ) documentation in the validation lifecycle. The information provided is intended to be helpful and practical for application in actual work situations. “PQ Forum” has addressed the following topics

1. *Validation Report Conclusion-Is it Validated?* Journal of Validation Technology *(*JVT*), Volume 16, Number 3, summer 2010.*
2. *Validation Equals Confirmation.* JVT*, Volume 16, #4, autumn, 2010.*
3. *Responsibilities of the Validation Approval Committee.* JVT*, Volume 17, #1, winter 2011.*
4. *Lifecycle Approach to Process Validation.* JVT*, Volume 17, #2, spring 2011.*
5. *PQ Documentation-Three Simple Rules.* JVT*, Volume 17, #3, summer 2011.*
6. *Original Data Supporting PQ.* JVT*, Volume 17, #4, autumn 2011.*
7. *Sampling Pages.* JVT*, Volume 18, #1, winter 2012.*
8. *Results Pages.* JVT*, Volume 18, #4, autumn 2012.*
9. *PQ Initiation-What, Why, How, and What Else?* JVT*, Volume 20, #4, winter 2014.*

The topics and recommendations provided in the above have been useful to validation professionals. Quality and compliance personnel have also commented that the “PQ Forum” discussions are also applicable to many compliance situations. A summary of these past discussions is provided along with potential applications. Some of these include:

- Quality and compliance documents require clear and decisive concluding statements
- Approvers of documents must review them with the perspective of a regulatory auditor
- The lifecycle approach-design and develop, demonstrate acceptability, monitor and maintain-has application to many quality and compliance activities as well as organizational processes
- Quality and compliance documentation must be clearly written, “stand alone,” and have good grammar
- Original data supporting quality and compliance activities must follow good documentation practices
- Complex sampling protocols and associated results may be facilitated by use of designed sampling and results summary pages.

INTRODUCTION

“PQ Forum” is an ongoing feature in the *Journal of Validation Technology* that provides a forum for validation practitioners to share information about Stage 2 Process Qualification (PQ) in the validation lifecycle. The information provided is intended to be helpful and practical for application in actual work situations.

Quality and compliance professionals from multiple companies have also commented that the problems identified in PQ Forum are the same as faced by quality and compliance professionals, and that the problem solutions proposed may be useful in applicable quality and compliance documentation. Quality documents include high-level discussions of policy, philosophy and beliefs, strategy, justifications, and rationale for the various aspects of the quality program. Batch records, justifications for deviations and non-conformances, CAPA investigations, product complaints, procedures, and other documents may benefit from discussions in PQ Forum. The quality of these documents is an extremely important element in the site quality program. Quality and compliance investigations may not be clearly written, present data ineffectively, and may not contain concise concluding statements. In all of these applications, sentence structure, grammar, and punctuation are vitally important. All these factors-fairly or unfairly-influence the judgments and interpretation by readers including regulatory agency auditors. They further influence perceptions of the associated organizations and individuals. Quality and compliance documents are often among the first documents requested in a regulatory audit-hence their importance in creating initial impressions that may persist throughout an entire audit.

The topics discussed, examples, information, and recommendations provided in “PQ Forum” have been provided by literally dozens of industry professionals from various disciplines during informal discussions at various IVT validation and related meetings over the past few years. These topics represent a consensus of frequently encountered problems and proposed solutions.

PQ FORUM #1. VALIDATION REPORT CONCLUSION—IS IT VALIDATED?

This discussion addressed a simple but significant problem with validation PQ documentation. Validation PQ documentation may lack a definitive concluding statement at the end of a validation report, i.e., the final sentence of a report is not clear and conclusive. This same problem may also occur in various quality and compliance documentation. All documents-validation, quality, and compliance-should finish with a definitive concluding statement.

In validation, the final sentence in a results discussion must clearly state whether the subject of the validation protocol has been successfully validated. It is insufficient to state “Results pass,” “Results met acceptance criteria,” or “Results OK.” There should be a discussion of results followed by a clear statement that the process, equipment, etc. of interest is validated. To not clearly conclude that the process, equipment, etc. is validated or qualified implies that something has not been completed or there is something wrong with the results. This omission reflects poorly on the writer on the validation group, on the site validation approval committee, and generally on the related organization. The validation report or results document is a key validation document that summarizes all test results as specified in the validation protocol. The validation report may also summarize results from multiple protocols in a more complex validation project. The final sentence in the results and discussion section should be a clear concluding statement. In many cases, scientists and engineers eloquently discuss results-but do not clearly state the ultimate conclusion for their work. The final sentence should be something like “These results indicate that _____ is validated.” Confirming that a process, equipment, etc. is validated through extensive testing specified in the protocol is the clear objective of the protocol.

Problem Example

The following is an actual regulatory audit experience provided by a validation manager. A regulatory auditor requested several validation packages associated with the manufacturing of a specific product for a pre-approval inspection audit. The process validation report for a specific product, the cleaning validation for this same product, and the equipment qualification report for the tablet-compressing machine were requested. All documents were quickly obtained from the validation library. These documents were recently prepared and were approved internally by the site validation approval committee. The auditor reviewed the lengthy validation report involving multiple manufacturing unit operations with testing numerous product attributes. After paging through 50+ pages of data and narrative, the auditor asked, “So is the process validated?” There was no concluding statement.

The report did not explicitly state that the process was validated. It did state that test results “passed,” but did not discuss data variation, individual data failures, retest results, or other problems. The main problem was that it did not clearly state that the process was validated-suggesting to the auditor that there may have been problems in meeting protocol acceptance criteria. Because this final conclusion was not clearly stated, the auditor and the QA manager reviewed nearly every page of the results report evaluating data, checking consistency with laboratory data, noting outliers, and generally reviewing all test results. The auditor suspected that since the reports did not explicitly state that the process was validated, there must have been failures in testing. The auditor was eventually convinced that the above results were acceptable and all validations had been successful. Extensive time (hours) and effort had been wasted, however, in reviewing all data in the documents-all prompted because the key concluding statement was not explicitly written.

Problem Solutions

Several suggestions were recommended to address this problem. These included a validation report template with concluding sentences and training for document writers and document approvers. A designated space for a conclusions statement to be added to the validation results template was proposed. This approach clearly indicated that a final validation conclusion statement is needed, and prevented the writer from forgetting to write the concluding statement. For example, a statement such as

“Results indicated that _____ is validated”

is typed into the validation conclusion section of the template. Another approach required the author of the report simply circle the appropriate response, such as

“Do results indicate that the process is validated? Yes No (Circle appropriate response)”

Either of the above should prompt the author to provide a specific concluding statement, and prevent the omission of this final statement. Sufficient training of protocol authors on the above would be part of the above approaches.

Application to Quality and Compliance

Although this PQ Forum addressed a problem specific to validation PQ documentation, it may be broadly applied to essentially every technical, quality, or compliance report. Reports must definitively state a conclusion at the end of applicable documentation. To present data and explain results without a definitive conclusion is a clear deficiency. The specific problem described involves only one sentence-the conclusion drawn from the results of validation work. Writers of quality and compliance documents must also write a clear concluding statement. The absence of a specific and definitive concluding sentence renders the document incomplete. A document is deficient without a meaningful final conclusion for the project. Without a clear definitive statement, questions remain in the mind of the reader-an undesirable lasting impression.

PQ FORUM #2. VALIDATION EQUALS CONFIRMATION

This PQ Forum discussion specifically addressed FDA expectations for process validation that may be a subject of debate in certain organizations. Validation PQ is expected to be confirmatory, i.e., the validation is expected to confirm the design, development, and other support work associated with the respective validation. Personnel involved in validation may not know or understand current validation expectations. Validation documentation may also be substandard due to incomplete development work. A strategy to change erroneous understanding of validation and define current validation expectations is proposed. The site validation policy should clearly state the site strategy and approach to validation and qualification.

Appropriate personnel should be trained on this policy. If there is not complete confidence in the future success of the validation PQ, protocols must not be approved and validation should not be initiated. The site Validation Approval Committee (VAC) should have significant input into development of the site policy and must then uphold the stated validation standards and expectations. The VAC should function as a surrogate regulatory auditor when reviewing and approving validation documents.

Validation has evolved over the years. The 2011 FDA Process Validation guidance (1) clearly states the current expectation for PQ. There is clear evidence that FDA expects manufacturers to thoroughly understand the process and confirm its acceptability in the PQ. The PQ is expected to confirm the design, development, and other preliminary work associated with the validation. The confirmatory PQ is a decision point that heavily contributes to the judgment to transition responsibility for the process from development to manufacturing for routine use. A successfully completed PQ is a strong statement that development of the subject operation has been completed and is ready for manufacture of commercial product. The most effective way to demonstrate readiness for routine use is through a successfully executed PQ-problem-free and mistake-free-which clearly shows that the design and development objective has been achieved.

Problem Solution

There are several reasons why the validation PQ is not always confirmatory. The primary reason is that people involved in the work of validation-R&D and development scientists, engineers, and other technical people - are not aware of current regulatory expectations. Validation is performed in different areas on different things related to manufacturing – manufacturing processes, cleaning processes, analytical methods, equipment, HVAC systems, water systems, computer systems, and so on. Each of these is performed by people with different expertise, knowledge, and experience. These people have different levels of awareness of regulations and regulatory expectations for validation. Other factors may also influence the validation approach. Project timelines may cause an accelerated initiation of validation. Commercial demand requirements may also cause validation to be prematurely initiated. New API or other materials may not be available to perform experimental runs prior to validation. Costs may be prohibitive, especially when used material will be destroyed and not commercially distributed. All personnel involved in validation must clearly know that validation is intended to confirm that the process, equipment, facilities, etc. is well understood, under good control, and can be expected to perform reliably and consistently throughout its respective lifecycle.

Validation managers suggested the following to educate personnel regarding contemporary expectations for validation:

- Validation policy: The site validation policy should clearly state the site strategy and approach to validation and qualification. These expectations should require that validation protocols contain requirements that are based on scientific and technical work done in advance of validation. Design and development work must be completed before validation is initiated. The validation should then confirm the design and development work. No optimization, fine-tuning, or other development work is allowed to be done in validation.

- Validation training. Validation training of appropriate associated personnel must be conducted. These included manufacturing, quality assurance, technical support, engineering, and other groups. Personnel involved in support work that is done preliminary to validation are key participants in this training. They must clearly understand that their work must be completed before starting validation, and that validation must confirm their work. This training will be especially useful to personnel who had learned validation many years ago but had not remained current with new developments or regulatory expectations. Management must be part of this training and support compliance to the policy.

- Validation Approval Committee. The site VAC has an important role in the site validation program. They have responsibility for approving validation protocols, results packages, and other associated documents. These documents must be in compliance with the site policy. Standards upheld by the site VAC sends a strong message to those who are responsible for development work and writing protocols.

- Pre-work, experimental studies, and engineering studies. Personnel initiating validation must be completely confident of the future success of their protocols. When personnel submitting protocols are not highly confident of future success, protocols must not be approved and validation should not be initiated. Additional development work may be required to address unanswered questions. Laboratory experimental studies, pilot scale work, or even full-scale trials may be warranted depending on the information available or risk of failure.

Application to Quality and Compliance

The above discussion may be applied to quality and compliance activities in situations where project work is also expected to be confirmatory. Documents or sections of document that are intended to confirm the adequacy of a process, corrective action, or complaint investigation should be written with an expectation of success. In the same way that validation is expected to be confirmatory, i.e., the validation exercise is expected to confirm the adequacy of prior experimentation, scale-up, and other development work, applicable quality and compliance documents must be prepared following the same approach.

PQ FORUM #3. RESPONSIBILITIES OF THE VALIDATION APPROVAL COMMITTEE

Manufacturing sites commonly have a Validation Approval Committee (VAC) that reviews and approves validation protocols, validation results, process and equipment changes, and related documentation. The VAC is a multidisciplinary group with representation from Quality Assurance, Manufacturing Operations, Engineering, Product Technical Support, Analytical, Microbiology, Regulatory Affairs, Validation, and other groups as needed. Quality Assurance representatives approve all documents. Other representatives review and approve documents as needed in their area of expertise and responsibility. For example, the regulatory representative reviews and approves product change protocols. The regulatory representative verifies that there is no impact on regulatory filings, and if needed, the regulatory representative initiates the appropriate regulatory submission. The engineering representative reviews and approves specific manufacturing equipment change requests for which he has expertise; the microbiology representative would usually not review and approve such changes. The VAC must review and approve validation documents at as needed at *ad hoc* meetings, at regularly scheduled VAC meetings, or through electronic document distribution systems.

Responsibilities of the VAC

The role of the VAC is extremely important. The site validation function depends on the judgment and decisions of the VAC. The VAC has three primary responsibilities:

- Technical excellence. The VAC must assure that all validation/qualification conducted is based on scientific and technical principles. All validation must confirm that processes, equipment, utilities, etc. are performing based on scientific and technical principles. There should be a consistent approach in the performance of validation. This approach should be based on risk to patient, product, and process. Rationale for the selection of tests conducted in the validation/qualification must be provided. Required sampling must adequately test processes, equipment, and systems to confirm acceptability in routine manufacturing in quantity of samples and duration of testing. Rationale for the sampling conducted in the validation / qualification must be provided. Equipment operating ranges must be qualified. Supporting documents are considered to be part of validation documents and provide a more complete technical justification for the validation.

- Compliance. The VAC must assure validation is compliant with relevant site or corporate policies, regulatory standards, and industry expectations. Validation performance must be compliant with internal policies such as site policies and corporate policies. Validation performance must be compliant with FDA and international regulatory guidances as is appropriate for the manufacturing site. Validation performance must be compliant with industry standards.

- Documentation. The VAC must insure that validation documentation must demonstrate the technical and compliance aspects in a logical and grammatically correct manner. Validation documents must demonstrate scientific and technical approach. The scientific and technical principles which are the basis for the validation / qualification should be adequately explained in validation documentation. Validation documents must be written clearly and logically, and must be written for the future reader of the document. There must be adequate evaluation and meaningful discussion of results. Validation documentation must be grammatically correct.

There must be a clear understanding and agreement among VAC members and the validation group as to their functions and responsibilities. Clearly stating the responsibilities of the VAC provides focus and expectations for the VAC. The objectives

clearly state the areas for which the VAC has responsibility. Clearly stating the responsibilities of the VAC provides clear expectations and standards for those submitting protocols, validation plans, and other documents for VAC review and approval. Members of the VAC must have the knowledge, experience, maturity, and training to fulfill the responsibilities of this position. VAC membership is not appropriate for new or inexperienced employees. The VAC must make decisions with the wisdom to understand potential consequences of their decisions.

Application to Quality and Compliance

These same considerations described for the Validation Approval Committee are relevant to approvers of applicable quality and compliance documentation. The VAC must consider themselves to be a surrogate FDA (or other regulatory agency) auditor. Approvers of quality and compliance documentation should have this same responsibility. They should review documents without input from the authors. Quality and compliance documents need to be “stand-alone” documents that can be understood by auditors without questions. If the author of a protocol must be present to explain the document to the approver, the document does not contain sufficient information or is not clearly written. Quality and compliance documents must contain sufficient information for future audit by external auditors. Approver responsibility is to review and approve documents that will be able to withstand scrutiny by regulatory auditors years into the future without explanatory input. Quality and compliance documents must be clear and concise. A document that “stands alone” and does not require verbal explanation to be understood is mandatory. Approved documents must not have obvious grammatical deficiencies. The approvers of quality and compliance documents must ensure that the above requirements are met and be accountable for the quality and audit readiness of these documents.

PQ FORUM #4. LIFECYCLE APPROACH TO PROCESS VALIDATION

FDA issued “Process Validation: General Principles and Practices” in January 2011. This guidance has given widespread visibility to the lifecycle approach concept. Validation managers are now responding to questions and comments about the guidance from their colleagues. These are relevant “hands-on” questions from people on the “front lines,” i.e., they face validation problems every day. Topics addressed in this discussion include:

What’s Different About The Lifecycle Approach?

The January 2011 process validation guidance (1) has integrated information, strategy, and approaches discussed in various US and international documents in past years to provide a comprehensive approach to validation, i.e., the lifecycle approach. The guidance has also provided specific and detailed recommendations for each stage of the lifecycle approach. The definition of process validation stated in the new guidance is as follows:

“Process validation is defined as the collection and evaluation of data, from the process design stage throughout production, which establishes scientific evidence that a process is capable of consistently delivering quality product. Process validation involves a series of activities taking place over the lifecycle of the product and process.” (1)

The approach to process validation stated in the 2011 guidance clearly emphasizes contemporary concepts and expectations for pharmaceutical manufacturing. The manufacturer should have great confidence that the performance of manufacturing will consistently produce APIs and drug products meeting expected attributes. This confidence is obtained from objective information and data from laboratory, pilot, and commercial-scale studies i.e., the work of Stage 1. After completion of Stage 1 development, Stage 2 Process Qualification confirms the work of Stage 1. After successful Stage 2 performance, Stage 3 Continued Process Verification maintains the validated state. As clearly stated in the guidance:

“The lifecycle concept links product and process development, qualification of the commercial manufacturing process, and maintenance of the process in a state of control during routine commercial production. This guidance supports process improvement and innovation through sound science.”

Successful validation depends on knowledge and understanding from product and process development. Specific key areas mentioned in the guidance include:

- "Understanding the sources of variation
- Detect the presence and degree of variation

- Understanding the impact of variation on the process and ultimately on product attributes
- Control the variation in a manner commensurate with the risk it represents to the process and product."

Why the Lifecycle Approach?

For manufacturing processes to be truly validated, each of the above stages must be addressed and integrated. This integration of development work, process conformance, and continuing verification provides assurance the product / process will consistently remain in control throughout the entire product lifetime. Process validation must not be considered a one-time event or a focused one-time task performed just prior to commercial launch that emphasizes only the manufacture of three conformance lots. Acceptable manufacture of three conformance batches must not be interpreted as completion of validation. These lots cannot truly represent the future manufacturing process with unexpected and unpredictable changes. Conformance lots are often inadvertently biased, *i.e*., they may utilize well characterized and controlled API and excipients, be manufactured under well-controlled conditions, be monitored by expert individuals, and performed by most experienced or well-trained personnel – all "best-case" conditions. It is highly unrealistic to contend that the manufacture of three conformance lots under "best–case" conditions conclusively predicts successful manufacturing over the product lifetime. True process validation must be a process that is never completed and is always ongoing.

Stages of the Lifecycle Approach

The guidance describes process validation activities in three stages:

- "Stage 1 – Process Design: The commercial process is defined during this stage based on knowledge gained through development and scale-up activities. This stage phase may be generally described as "process understanding,"- studies conducted to understand product and process. The work of Stage 1 should be commensurate with the identified or expected risk for the product and process. Stage 1 recommendations address development activities that will ultimately be reflected in the master production record and control records. The guidance clearly states the goal of stage 1: "To design a process suitable for routine commercial manufacturing that can consistently deliver a product that meets its quality attributes."

- Stage 2 – Process Qualification: During this state, the process design is confirmed as being capable of reproducible commercial manufacturing. This stage may be simply described as "validation performance." This stage is most similar to the traditional definition and performance of validation. The testing of Stage 2 should be commensurate with the risk identified for the product and process. The Stage 2 Process Qualification stage comprises demonstration of commercial process performance by means of conformance lots. This stage confirms the development work of Stage 1 Process Design. Successful Stage 2 performance demonstrates that the proposed manufacturing process is capable of reproducible commercial manufacture. Process Performance Qualification (PPQ) conformance lot manufacturing includes increased testing to demonstrate acceptability of the developed formulation and process.

- Stage 3 – Continued Process Verification: Ongoing assurance is gained during routine production that the process remains in a state of control. This stage may be simply described as "maintaining validation," or "maintaining the validated state." Maintenance activities of Stage 3 should be commensurate with the risk identified for the product and process. Assuming good development of the process, identification of potential variation, and control of same, the manufacturer must maintain the process under control over the product lifetime, i.e., the work of Stage 3. This control must accommodate expected changes in materials, equipment, personnel, and other changes throughout the commercial life of the product and do so based on risk analysis.

The above clearly identifies the key difference between the lifecycle approach compared to validation in the 1987 FDA guidance. The 2011 lifecycle approach to process validation encompasses product and process activities beginning in development and continuing throughout the commercial life of the product. The 1987 definition and subsequent discussion in the guidance placed major emphasis on the validation protocol, testing, results, and documentation – what is now considered to be Stage 2 in the lifecycle approach. Development work and post-validation monitoring were not emphasized in the 1987 guidance (2).

Application to Quality and Compliance

The concepts identified in the respective stages of the FDA process validation guidance – process design (understanding), process qualification (performance), and continued process verification (maintaining validation) – serve as a model for all

areas of quality and compliance in the organization. The sequence of understanding, performance, and maintaining the validated state is certainly applicable and desirable for other processes in pharmaceutical manufacturing including packaging, cleaning, analytical, and so on. Further applying this sequence to equipment qualification, HVAC, computer systems, and other areas is also appropriate and desirable. Presentations on these associated topics at validation meetings have already been structured according to this model. The ISPE IQ/OQ/PQ model and the ASTM E2500 model are consistent with understanding, qualifying, and maintain qualification through calibration, preventive maintenance, change control, and associated activities. Quality systems may also be managed according to the lifecycle model. Quality systems should be appropriately designed and developed, demonstrated to perform as designed, and monitored to maintain performance. Improvements in quality systems should occur as experience is gained. Applying the stages 1, 2, and 3 sequences of activities to appropriate quality and compliance activities unifies the site approach to project management activities, standardizes expectations, facilitates training, and generally simplifies organizational thinking.

PQ FORUM #5. PQ DOCUMENTATION—THREE SIMPLE RULES

Validations managers identified validation PQ documentation problems as one of their most troubling problems. Documentation problems are prevalent at all stages of PQ – plans, protocols, and results. Problems generally included incomplete and inadequate content, explanations that are not thorough or understandable, and incorrect grammar and spelling. Documentation problems may have very significant consequences including serious negative impressions on auditors.

The problems described did not violate corporate policies or site procedures. Documents were approved by the site approval board including QA, but did not meet standards or expectations. The writers of documents were educated in science and technology and in many cases had advanced degrees. Despite their education and credentials, their written documents were often substandard. These problems occurred at all stages of PQ - Validation initiation and plans, validation protocols, and validation results/reports.

Three categories of problems were identified by validation managers:

- Incomplete and inadequate content. A major problem described by validation managers involved the content of the validation document. Originators of validations and qualifications knew the objective of their projects. However, their documentation often did not clearly or completely address the objective. Further, their focus was often inconsistent throughout the sequence of validation documents. Deficiencies described ranged from gross omissions to poorly described details. Many problems with original data recording including destruction of original data, number transpositions, and other problems were described.

- Explanations not thorough and not understandable. Another major problem described by managers was inadequate discussion of validation results. Validation documents are read by people with varying technical backgrounds and varying levels of education and experience. Auditors who are trained and experienced in analytical chemistry may audit manufacturing process/equipment validation documentation. Or conversely, auditors with little chemistry background may review and critique technical analytical methods. Validation writers often tend to write as little as possible. They argue that writing minimal content will prevent regulatory observations – “the more your write, the more you will be gigged.” Also, personnel doing validation work are often more oriented to “doing” rather than writing – they do not enjoy writing; when forced to write documents, they provide minimal content documents. At the other extreme are writers who write too much and provide excessively lengthy documents. Their strategy is to provide documentation which is so voluminous that it cannot possible be read by the auditor – and hence will not be reviewed and no regulatory observations will ensue. Both of these approaches are flawed. Another problem expressed by validation managers involved the level of technical content of validation documents. Some writers write at a high level of complexity rendering their documents not understandable to others outside of their academic discipline. Validation documents must not be so complex that they are understandable only by the author or by a reader with a high level of related expertise. At the other extreme were situations in which writers of validation documents helped explain the content to the site validation approval committee during the approval process. While this practice is helpful and facilitates approval, it inadvertently creates substandard documents. Written documents must be understandable without additional expert explanation.

- Incorrect grammar and spelling. Validation managers also complained about poorly constructed sentences and

spelling mistakes. The content of validation documents must be correctly written. All agreed that the technical writing skills are not something to be assumed. People who are technically knowledgeable, or are good verbal presenters of information are not necessarily good writers. People with advanced degrees should also not be assumed to be good writers. Spelling mistakes were also very common despite automatic spell check in word processing programs. Validation documents must contain correctly structured sentences, and incorrect spelling must not be overlooked.

If validation documents omit results, have either insufficient or excessive levels of content, or contain grammatical or spelling errors, the reader will infer a negative impression. This impression will include the specific functional organization responsible for the document and the author. Good work may be unfairly evaluated because documents were poorly written. The impressions provided by poorly written or sloppy documents may negatively influence a regulatory auditor and may carry over to the entire site and other specific areas during the audit – with very serious consequences.

These same considerations are applicable to quality and compliance documentation.

Problem Solution

This issue proposes three simple and memorable rules are proposed for validation documents. These are:

- Clear, complete, concise, and consistent
- “Stand-alone” documents written for the reader
- Short sentences and simple words.

Clear, complete, concise, and consistent. The respective content of the validation documents should be clearly and directly related to the objective of the document. There must be definite continuity between documents. The content of the sequence of PQ validation documents – validation initiation and plan; validation protocol, and validation results/report - must demonstrate knowledge and understanding, must be relevant to the objective, and must be clear, concise, consistent, and complete. There should be a logical progression of information throughout the sequence of documents. Stage 1 documents – design and development - should demonstrate good understanding of the system being validated. Design and development work should be based on scientific and technical principles. They should identify highest risk areas. They should address sources of variation and provide control mechanisms. Statistical methods should be used for decisions whenever possible. The content and recommendations of Stage 1 documents should then be reflected in Stage 2 PQ validation documents. Stage 2 Validation PQ documents should be consistent with information developed in Stage 1, describe systems and risks, and identify appropriate testing and sampling based on risk analyses. Protocols should detail testing as recommended in plans. Tests must be executed based on specified details in protocols. Results and reports should clearly discuss confirmatory results and clearly state whether the system is validated. Stage 3 documents should demonstrate the ongoing maintenance of the validated state as designed in Stage 1 and executed in Stage 2. Systems must be monitored based on risk. Highest risk areas must receive greatest attention in sampling, testing, and frequency of same in Stage 3. If changes to validated systems are required, they should be evaluated through a change control system that follows a Stage 1-Stage 2 progression of analysis and execution.

“Stand-alone” documents written for the reader. Stand-alone documents must provide thorough and understandable explanations. Validation documents must be written for the future reader of the document. Validation documents will be read by a wide variety of readers over the many years that they will be relevant. Individuals with varying backgrounds, education, experience, orientation, and so on may potentially read validation documents. Authors of validation documents must try to write documents that will be understandable to all of these potential readers. Colleagues from other areas (with unrelated expertise) should be asked to review documents to help gauge the acceptability of discussions. Documents that clearly require additional explanation to be understood are not acceptable - Documents must “stand alone.” Input from the site validation approval committee, i.e., multidisciplinary individuals with varying backgrounds, should be helpful in developing an appropriate level of explanation in the validation document. When reviewing validation documents, the validation approval committee must “eschew obfuscation and espouse elucidation,” i.e., documents must be clear and understandable. The content of the document must be understandable to the future readers of the document.

Short sentences and simple words. Validation documents must be correctly written following conventional rules of grammar and punctuation. There must be no spelling errors. There is no excuse for grammar and spelling errors in a modern technical organization. Sentences should be short and simple. Too many phrases or and an excessive number of commas in a sentence likely indicates a poorly constructed sentence. Simple words should be used whenever possible. The reader will not be impressed with complex words if the content is not understandable.

Writers of validation documentation must be trained. They must understand validation fundamentals as well as the importance of their documents. Their documents must meet the above three rules. The site Validation Approval Committee (VAC) must be supportive of good validation documents and must maintain appropriate standards for document approval. Substandard validation documents reflect poorly on the organization and on the writer.

Application to Quality and Compliance

Quality and compliance documents are critically important. These documents are always reviewed by regulatory auditors. Documentation problems observed by regulatory auditors may have very significant consequences – even beyond the specific area of interest. Organizations should be whatever is necessary to maximize the quality of quality and compliance documents.

Three simple rules are proposed for writers of validation documents are applicable to appropriate quality and compliance documents. Improving quality and compliance documentation cannot be achieved solely by the effort of the site quality group. Training of all site individuals with involvement in quality documentation is recommended. Templates and model documents should be developed to establish standards. Writers of documents must be made aware of the importance of their documents. They must understand basic fundamentals as well as regulatory requirements and expectations for documents. Document approval personnel must also insist on good documentation. They must consistently maintain the established standards for their respective documents.

PQ FORUM #6. ORIGINAL DATA SUPPORTING PQ

This discussion addressed various problems with validation documentation regarding data contained in validation reports and associated documents. This discussion is especially relevant since Stage 1 development data is becoming an important part of PQ documentation and must directly support PQ documents.

The data reported in validation results are key components of a validation project. The protocol specifies required sampling and testing that in turn generate data. The validation report reproduces these data, discusses results, and provides conclusions. The respective content of the original data, protocol, and results must be consistent to demonstrate that the item of interest is validated. Test data and results generated as specified in the protocol are critical in the validation process because they provide the technical basis for the final validation report. Data in the validation report must also be consistent with development data that support the validation project. R&D and other technical reports may be referenced in the validation report.

The acceptability and integrity of validation data determines whether or not a process, equipment, utility, etc. is validated. Everything depends on acceptable test results and data integrity. Further and more important, problems with reported data may seriously impact the credibility and reputations of associated individuals and management in the organization.

The data and documentation problems described above may be grouped into the following categories:

- Original data practices. Validation managers reported numerous problems with original data. Some of these include data recording on individual pieces of paper, i.e., loose, unbound or unattached paper. Data may remain on these sheets, or may be copied into laboratory notebooks or other documentation systems. If transferred to other systems, the original data sheets are usually discarded. People recording data do not understand that where they originally record data is a primary document that must be retained. Validation managers described events in which test results were written on paper bags and paper towels. Data corrections such as by “scratch-outs,” “cross-outs,” using “white out” correction liquid, and other means. These events demonstrated gross misunderstanding of good data and documentation practices.

- Original data responsibility and verification. Inadequate personal signature/date when recording data, inadequate verification, inadequate approval. Also there was no verification of data by a second person. Examples described above (individual pages, paper bags, and paper towels) were not signed / dated by the technician nor were pages verified by a second person. Without verification by a second person, there is no assurance that the work was actually done and was not falsified data. There is no proof of performance.

- Data in reports. Data errors in reports due to number transpositions and other problems such as inadequate review of data against original data were reported. One manager described an event involving an FDA submission where more than 25 errors were found – number transpositions, e.g., original 45 written as 54; wrong numbers, and other problems. Carelessly written original numbers contributed to the problem, e.g., a carelessly written “6” was read as “0”. The magnitude of the errors was not sufficient to change the interpretation of results. Still, however, the final validation report did not accurately reflect the actual test data. Data transferred to the validation report was not checked for accuracy. There were no signatures by personnel responsible for data transfer or verification of the data by a second person. Checking data transfer is tedious work – not something that can be done quickly or with a superficial approach. An FDA-483 observation was given by the investigator who found the errors.

- Data accuracy. Reports must be free of errors, number transpositions, or other mistakes. When small amounts of data are being reviewed, all data must be checked. When large volumes of data are being reviewed, a reasonable sampling of data will be adequate. These approaches should be defined in a site SOP. Whomever does the data transfer must verify the transferred for accuracy. This person should also sign / date that data transfer accuracy has been verified.

- Data consistency. Validation managers commented that often original data undergo multiple transfers between the original work and final reporting in a validation document. For example, original solubility data for an API was determined in an R&D lab at the start of a development project. This determination was referenced several times during the development program in multiple reports and emails. Ultimately the cleaning validation results package that was conducted several years after the original solubility work referenced these same data. Through these transitions, experimental details were lost, numbers were rounded, values were approximated, and so on. The value reported in the cleaning validation was different than the original experimental determination even though each individual transition was reasonable and defendable. When a new report is written, data should be reviewed for consistency starting with prior data.

- Data retrieval. Original data must be retrievable, and must be retrievable within a reasonable time period. Another validation manager described an incident whereby a validation report for equipment was requested by an auditor. The validation report was more than ten years old. The report contained typewritten data on machine operational parameters and material test data. The auditor asked to see the original test data. The engineer who authored the report had left the company several years ago, and his experimental files were in company archives at another site. All other persons involved in the original validation (QA, engineering, and other groups) were also no longer with the company or in other jobs at other company sites. There was no way to easily retrieve original data or get information about the project from individuals involved. Original data must be rapidly retrievable if requested during an audit or to review technical content. “Rapid retrieval” means within 30 minutes. If data or reports are not able to be retrieved within 30 minutes, the auditor should be advised as soon as possible. Audits conducted at manufacturing sites in Puerto Rico may require data from corporate facilities in the US; often these connections cannot be made in a timely manner. Validation managers should consider insisting on filing original data or copies of data in the validation library when retrieval systems are not automated or electronic.

Quality and compliance documents and reports may have the same problems as indicated above.

Problem Solutions

Validation managers suggested solutions to address the above data and documentation problems. Specific recommendations included:

- Data recording and data storage systems. All original technical data generated in an organization must be recorded into a system that is secure, retrievable, and protective of data integrity. The system must allow data to be retrieved as needed within a reasonable time period. Data may be recorded into bound laboratory notebooks or into electronic systems. Electronic systems are desirable; then provide security and enable immediate access. Rapid retrieval of data is especially important when requested by regulatory auditors. Data may be recorded into bound laboratory notebooks

with consecutively numbered pages. Numbered pages are required to prevent pages from being removed from the notebook. Three-ring binders with loose pages are not suitable for use as laboratory notebooks. Filled notebooks and notebooks belonging to personnel who have left the organization should be stored in a secured area. If notebooks are removed from the secured area, there must be a mechanism to return the notebook to the area, i.e., unrestricted access and removal of information is not acceptable. R&D scientists are accustomed to using laboratory notebooks. Systems in which technical personnel are assigned specific number individual notebooks can be easily implemented. A notebook administrator at the site should be designated. The notebook administrator is responsible for tracking all notebooks at the site. Notebooks assigned to technical personnel are used and stored by them in their offices or laboratories. They should be stored in locked desks or other secure locations. When individuals who have notebooks leave the organization, they must return the notebooks to the site notebook administrator. This enables all data in the notebook to always be accessible to auditors or for other needs. Manufacturing sites may not be familiar with these practices and not have secure systems in place. Even worse, they may be resistant to implementing even simple notebook systems. Groups may believe that documentation procedures are not important or are too restrictive to their regular responsibilities. These erroneous attitudes must be immediately addressed and corrected. Original data cannot be recorded on scrap paper and stored in a personal desk drawer in a compliant organization.

- Good data and documentation practices, including data responsibility, corrections, and associated practices. Data and documentation practices must be defined in procedures. This applies to signatures, initials, dates, correcting errors, explaining errors, dating practices, and other procedures associated with data recording and verification. These practices are usually well defined in manufacturing and quality organizations. Related organizations, i.e., those not directly involved in daily GMP activities, may not have rigorous documentation procedures. More importantly, management of these organizations and the culture of these areas may not emphasize the importance of good documentation practices. Organizations even remotely connected to GMP activities must have procedures defining these practices. Personnel must understand and be compliance with procedures. Whenever data are recorded, the person recording the data must affirm the accuracy of the data and accept responsibility for the data. This is done by signature / date on the original data document. People must be accountable for their work. When they are required to sign/date documents or data affirming the performance of their work, the accuracy of their data, and so on, i.e., their personal integrity is behind the document, personnel reviewing the document have much greater confidence in the content of the document. Depending on the type and circumstances of the situation, original data should also be witnessed by a second person. Verification by a second individual may be likened to GMP requirements that critical steps in manufacturing must be verified by a second person. Verification by a second individual applies to original data recording as well as to data transfer from original data records to computer systems or to validation reports. If, for example, original data are entered into a spreadsheet for statistical analysis, original data entries on the printed spreadsheet must be verified for accuracy and affirmed by signature / date on the printout of the spreadsheet.
- Training. Training on good data and documentation practices is mandatory for all individuals involved in the recording, transferring, or approving data or reports containing data. The examples provided by validation managers indicated significant misunderstanding of fundamental procedures and serious non-compliance. Technical and engineering personnel are often not as familiar with data-recording procedures as manufacturing, QA or GMP analytical lab personnel. Procedures addressing data recording, signatures, dates, and so on may be infrequently used in their daily job functions. Training and periodic retraining must be considered depending on the overall competence of the organization. Individuals with good documentation skills may be assigned to work with personnel who are unable to meet training standards, i.e., a partnership approach to facilitate acceptable data recording. Some organizations have hired GMP specialists for this purpose. Multiple groups that must be trained on the above concepts include:
    - Personnel involved with data. This includes all personnel involved with data recording, transferring, reviewing, approving, etc. These people must be very familiar with good data and documentation practices.
    - Validation writers. This includes people who write validation plans, protocols, and validation results documents. The must know good data and documentation practices to assure that data contained in their documents are acceptable.
    - Validation Approval Committee (VAC). Validation Approval Committee (VAC). This group approves all written validation documents. They also must know good data and documentation practices to assure that data contained in the documents the review are acceptable.
- Validation Policy and Practice. Validation managers suggested development or enhancement of documentation practices associated with validation documents. Two practices were recommended:
    - Review of Original Data by the VAC During Validation Document Approval. When the VAC is reviewing a

validation report containing test data or other results, the documentation containing original data should be requested and must also be reviewed. This practice should be clearly stated in a validation procedure. Implementing this practice will eventually eliminate data recording on paper towels and similar unacceptable media. If original data are still recorded on individual sheets of paper, paper towels, or paper bags, these must be considered primary documents and be retained and stored appropriately. They must be reviewed in addition to the data provided in the validation report. VAC members who review and approve validation documents must not be completely dependent and trusting of the data typed into validation reports or other documents containing transferred data. Regarding transferred data, VAC members should also insist on responsibility (signature and date) of personnel who have transcribed data from original documentations to the validation report. Policies should specify requirements for data verification. All data numbers should be verified for small amounts of data. Reasonable sampling of data for verification is acceptable for large amounts of data. In any case, acceptance of transferred data in a validation report without verification must not occur in the approval process for validation documents.

- Storage of Original Data in Validation Files. Original data may be stored as part of the approved validation report in the validation library. The validation library should be a secure area from which validation documents cannot be removed. If a site does not have document storage system or a bound notebook system and is unwilling to implement such a system, storage of original data in validation documents should be done. The validation report must be supported by original data. If the site does not have a good data storage and retrieval system, the validation area should store the original data within the validation package. If originators are not willing to release their original data, the copies of original data should be filed with validation documents.

Application to Quality and Compliance

Quality and compliance data integrity is critically important. The problems described above and recommended solutions are applicable to quality and compliance data. Data and documentation problems are ongoing problems – they never go away. It is human nature to “cut corners,” bend rules, and so on in the interest of time or efficiency. Quality and compliance personnel should persist in encouraging electronic systems, optimized design of forms, and minimizing opportunities for personnel errors in data practices and documentation. Training is a necessity. Training must also be periodically repeated to emphasize and encourage proper practice. Quality and compliance personnel must continually be aware of the potential for documentation problems when personnel record original data.

PQ FORUM #7. SAMPLING PAGES

Validation managers identified problems with validation sampling as one of their most troubling problems in PQ execution. Missing validation samples are a troubling occurrence with potentially serious consequences. As sampling schemes become more complex, the incidence of missing samples increases. In addition to loss of information required in the validation protocol, missing samples requires investigation, documentation, explanation in validation reports, and usually an additional lot added to the validation package – extra work for validation as well as an embarrassment for the organization. An auditor who reads validation documentation describing missed sampling will be left with an unfavorable impression. If something as mundane as sampling cannot be successfully accomplished, what does that say about the other activities of the organization?

When sampling requirements are complex and there is heightened potential for errors, designated sampling pages are recommended. These pages clearly describe the samples to be withdrawn, list requested samples, and require signature /date of the sampling person. Diagrams or digital photos may be included. The pages provide a definite focus on the sampling process for personnel obtaining samples. Pre-printed labels, sampling containers, and other measures to facilitate sampling are also discussed.

Validation managers report that sampling specified in validation protocols may be omitted, overlooked, or incorrectly executed during validation performance. This problem most often occurs in complex sampling schemes. The problem also occurs when inexperienced operators are involved in the validation and are confused by the extra samples required for validation. It also occurs when conformance runs are infrequent, i.e., the extra sampling requirements do not occur often and personnel simply do not remember what to do when additional samples are required.

The consequences of missed samples may be significant. In some cases, missing samples are able to be retrieved from

manufactured materials, i.e., the integrity of the samples obtained later is same as samples obtained at time of execution. However, in other cases, equivalent samples may not be available. For example, when future unit operations in a manufacturing process change the prior samples properties or composition, the samples required for validation are not able be retrieved. Missing samples cause loss of required information. Missing samples may impact specified data treatment. Missing samples must be explained in the validation results. In some cases, when significant numbers of samples are missing, an additional conformance lot may be required to accomplish the intent of the validation. For example, one validation manager described a commercial scale tablet manufacturing lot in which multiple samples were required from each of eight drying runs. The eight runs were then blended together to continue the process, i.e., the individual drying run identity was lost. No validation samples were withdrawn during the drying process. When the omission was discovered, an additional conformance lot was then added to the protocol to replace the lot that was not sampled and thus confirm acceptable drying process performance.

Quality and compliance projects with complex sampling may also benefit from the proposals recommended for validation sampling.

Problem Solution

Several validation managers described their use of designated sampling pages when sampling requirements are complicated and have potential for mistakes and omissions. These pages are constructed at the time of protocol preparation and are included in the approved validation protocol. They are printed on colored (pink) paper to stand out from the other pages of the protocol. These pages clearly describe the samples to be withdrawn, list requested samples, and require signature /date of the sampling person. Digital photographs may be included on sampling pages. The pages provide a definite focus on the sampling process for personnel obtaining samples. The site Validation Approval Committee approves the sampling pages at the time of protocol approval. Pages are then provided to the manufacturing area. Pages are used at the time of sample withdrawal. Training of the sampling person is also provided as needed. In some case such as blend uniformity sampling using a sampling thief or sterile process sampling requiring aseptic technique, sampling is done only by a qualified sampling person who has undergone specific training. Completed sampling pages are ultimately returned to the validation areas and are part of original validation documentation. An example sampling pages is presented in Table 1.

Application to Quality and Compliance.

Samples are critically important in the execution of applicable quality and compliance projects. Missing samples may have serious ramifications for the validation exercise and for the organization. When sampling requirements become complex and have potential for errors or omissions, specific and prominent sampling pages are recommended. These pages contain all relevant sampling information, list-required sample, and may include diagrams or photos to support correct sampling. They are designed with consultation from the users, i.e., designed with the customer in mind. Sampling pages are then used during the sampling process. Pre-made labels and appropriate containers for samples should be available at the start of sampling. A storage container to contain all labels, materials, and withdrawn samples for transport to the test laboratory is also recommended.

Quality and compliance personnel must anticipate situations in which sampling problems may occur. Designated sampling pages have been suggested by validation managers to prevent sampling errors, omissions, and other adverse events. Pre-printed labels, designated sample bottles, and other measures to facilitate the sampling process are also recommended.

FIGURE 1.
PROCESS VALDIATION SAMPLING PAGE – OVEN DRYING

PROCESS VALIDATION SAMPLING

PRODUCT: _____
LOT # _____
VALIDATION # _____

UNIT OPERATION: Oven drying

SAMPLING: Withdraw 10-gram samples from middle of tray from top, middle and bottom of each cart.

		SAMPLE #	SAMPLED BY	DATE
CART #1	TRAY TOP	1	_____	_____
CART #1	TRAY MIDDLE	2	_____	_____
CART #1	TRAY BOTTOM	3	_____	_____
CART #2	TRAY TOP	4	_____	_____
CART #2	TRAY MIDDLE	5	_____	_____
CART #2	TRAY BOTTOM	6	_____	_____
CART #3	TRAY TOP	7	_____	_____
CART #3	TRAY MIDDLE	8	_____	_____
CART #3	TRAY BOTTOM	9	_____	_____
CART #4	TRAY TOP	10	_____	_____
CART #4	TRAY MIDDLE	11	_____	_____
CART #4	TRAY BOTTOM	12	_____	_____

Drying Cart

Digital photo of drying cart identifying top, middle, and bottom trays

Drying Tray

Digital photo of drying tray identifying location of sample to be withdrawn (center of tray)

DELIVER ALL SAMPLES TO TEST LOCATION # ___

PQ FORUM #8. RESULTS PAGES

Results pages or data pages are a logical extension of sampling pages. Results pages were also recommended by validation managers during the discussion about sampling pages. These pages contain the associated test results. These pages also describe data treatment, provide “pass / fail” evaluation, and other features helpful for ultimate review and evaluation of the validation project. When extensive compilations of data are required in a project, results pages provide a helpful approach to record and present all data, support analysis and evaluation, and facilitate conclusions.

Validation managers commented that problems with validation results are a relatively frequent occurrence in the validation process. These problems potentially may have very serious ramifications. Problems with validation results may or may not be related to validation sampling. If validation sampling is not correctly done, test results will obviously be deficient. However, problems with validation results may occur even when sampling is correctly performed. Several categories of problems with validation results were described by validation managers:

- Results documentation. This includes missing results and disorganized results. When complicated sampling schemes are required, the laboratory may not test all samples or may test the same samples multiple times. Missing results due to missing samples is an obvious problem. Missing samples may not be able to be obtained if process samples are no longer available. Complicated sampling schemes may also result in disorganized tabulations of results, especially when labeling is unclear or analysts do not understand the sampling scheme.
- Results review. When data are missing or presentation of data is not organized, effective and accurate review and

approval of results is not possible. This problem is magnified as erroneous evaluations proceed through the system. Problems may occur in the test area, during technical review, and when validation documents are reviewed and approved.

- Data consistency. Original test data must be accurately transferred to results pages. Validation results data must be consistent with original laboratory test data. Original data practices, data responsibility and verification, data transpositions, and timely retrieval of data have been identified as problems with original data.

The consequences of the above results problems may be significant. Consequences may be specific to the individual data set. Consequences may also have greater impact on the entire organization, i.e., if something as simple as sampling, testing, and data reporting is not done correctly, what does that say about the entire organization and its quality systems? If results problems are observed early in a regulatory audit, unfavorable impressions may have a negative effect on other areas in the audit.

Problem Solution

Validation results pages are formatted pages containing test results from a validation-testing scheme. Validation results pages minimize various problems with validation results including missing results and disorganized results. Results pages also facilitate results review in the test area, technical review of results, and validation document review and approval. Validation results data must be consistent with original laboratory test data. Formatted blank validation results pages are constructed at the time of protocol preparation and are included in the approved validation protocol. Completed results pages are then part of final approved validation documentation. Figure 2 provides an example results pages for a drying unit operation.

Consistency with original data. Original data generated by the testing area must be consistent with results pages and must be reviewed. Problems reported included data recording on loose paper, paper bags, and paper towels, erroneous transcribed data – number transpositions, wrong numbers, carelessly written original numbers, no signatures by personnel responsible for data transfer or verification of the data by a second person, data responsibility, error corrections - “scratch-outs,” “cross-outs,” using “white out” correction fluid, etc., and other means. Data retrieval, data accuracy, “dry-labbing,” and other data integrity issues have been reported.

Application to Quality and Compliance

Results are critically important in quality and compliance documentation. Results may be repeatedly audited by domestic and global regulatory agencies during the lifecycle of the product, process, facility, etc. Anything that can help improve the various activities associated with data integrity and prevent potential problems associated with results should be strongly considered.

Results pages are a useful tool. Formatted blank results pages (no data) should be included in protocols and approved at the time of protocol approval. The format of these pages should be developed in concert with the testing area and the technical group. The testing area will record test results on these pages, perform calculations, and indicate pass/fail of results. The technical group will review and evaluate test data on results pages in the final validation report. The final report including the results pages will ultimately be approved.

Results pages clearly indicate missing results. Results pages help to organize data in a manner useful to the test area, technical group, and approval group. Results pages should enhance the technical discussion in the report and facilitate review by regulatory auditors. Data on results pages must be consistent with original data.

Results pages require time, effort, training, cooperation, and management support to initiate. However, once developed, results pages will become an automatic part of project documentation.

FIGURE 2. PROCESS VALDIATION RESULTS PAGE
DRYING UNIT OPERATION

PROCESS VALIDATION RESULTS

PRODUCT: _____
LOT # _____
VALIDATION # _____

UNIT OPERATION: Oven drying

TEST LOCATION # _____

TEST METHOD: Procedure XX-XX, approved date _____

SAMPLING
_____ gram samples from middle of tray from top, middle and bottom trays of each cart.

PROTOCOL ACCEPTANCE LIMIT: All results not more than ____%

		SAMPLE #	RESULT	PASS (circle)	
CART #1	TOP	1	_____	YES	NO
CART #1	MIDDLE	2	_____	YES	NO
CART #1	BOTTOM	3	_____	YES	NO
CART #2	TOP	4	_____	YES	NO
CART #2	MIDDLE	5	_____	YES	NO
CART #2	BOTTOM	6	_____	YES	NO
CART #3	TOP	7	_____	YES	NO
CART #3	MIDDLE	8	_____	YES	NO
CART #3	BOTTOM	9	_____	YES	NO
CART #4	TOP	10	_____	YES	NO
CART #4	MIDDLE	11	_____	YES	NO
CART #4	BOTTOM	12	_____	YES	NO

COMMENTS _____

RESULTS RECORDED BY _____ **DATE** _____
DATA TRANSFER VERIFIED BY: _____ **DATE** _____
RESULTS APPROVED BY _____ **DATE** _____

PQ #9. PQ INITIATION – WHAT, WHY, HOW, AND WHAT ELSE?

This discussion addressed problems associated with the initiation of PQ validation. Validation managers described problems clearly identifying “what” is being validated, “why” this work is needed, and “how” it will be successfully accomplished – the “what,” “why,” and “how” of validation. Problems with identifying additional activities to be addressed before validation, and activities to be done as result of validation – the “what else” of validation – were also mentioned as a significant problem. There are several reasons for these problems. Business reasons such as emergency situations, urgency to initiate projects, internal goals, project scope changes, and other circumstances may cause work to start before complete understanding of project requirements or effects on associated systems. New personnel, transferred employees, contract workers, and others with limited technical or validation experience may also contribute to these problems. PQ processes and documentation are often significantly impacted by these problems, in turn adding time, effort, and frustration to the validation process as well as impacting PQ documentation.

The following discusses the various approaches used in different companies to initiate PQ validation. The focus in this discussion is primarily administrative – officially initiating the validation project so that affected areas are mobilized as needed to support the validation. Especially important are initiating external activities where prior regulatory approval or state and local legal notifications may be needed. The approach described comprises the answers to four simple questions: “What, why, how, and what else?” A comprehensive approach to initiating PQ validation is vital to efficient project management and ultimate completion of the validation.

This same problem is a consideration in quality and compliance activities that are repetitive or generally initiated with the same

considerations. “What, why, how, and what else?” may be applicable to certain quality and compliance activities in the organization.

Initiating PQ Validation

Initiating PQ validation should be a simple and straightforward task. The following are fundamental components of the proposal to initiate PQ validation:

- What? What is being validated or qualified?
- Why? Why is the validation necessary?
- What else? Pre-validation activities. The performance of validation may require additional activities to be done prior to validation. These may be external or internal activities.
- How? How will the validation be accomplished? The approach to accomplishing the validation requires an impact analysis or risk assessment to determine the appropriate level of testing in the validation. The validation plan is then developed. This is the most critical component of the validation. The validation plan dictates the content of required protocols, sampling, and testing. The specifics of “how” – the validation plan - will be discussed in a future PQ Forum.
- What else? Post-validation activities. Additional activities may be required as result of the validation. These again may be external or internal activities.
- Approval. The above components of the validation initiation must be approved by appropriate members of the site Validation Approval Committee (VAC).

Every person who reads PQ documentation including regulatory auditors is interested in all of the above points. They expect these points to be clearly stated and directly addressed in the validation project. PQ documentation should reflect the clarity and simplicity of the above. Personnel who write validation documentation, approve validation documentation, or are responsible for validation documentation should have these issues in mind. The “what” and “why” questions should be easily and simply addressed. The “how” question is more complex, must be based on risk, and may be delayed until all validation details are known for complex projects “What else “ associated pre- and post-validation activities must be accomplished for external reasons, internal communication, and general project management and ultimate completion.

The problems identified by validation managers involved all of the above components of PQ initiation. Despite the simplicity and straightforwardness of the above, validation managers comment that personnel in their area do not consistently or completely address the above in their project activities and validation documentation. Some of the general problems mentioned by validation managers include the following:

- Inconsistent content. Different authors in an organization have different approaches to initiating validation.
- Poorly written – content, grammar, spelling, punctuation.
- Prematurely written. Documents may be initiated to meet business goals or written to demonstrate future intent.
- Omissions. Activities associated with the validation are often omitted or overlooked.
- Amendments. When the document is prematurely written, amendments will surely be required. Amendments may be necessary because of scope changes to the project – these are understandable and usually acceptable. However, amendments are often necessary because of inadequate planning or other failures – these are not acceptable and reflect poorly on the entire organization.

Problem Solution

This discussion has provided a simple outline of required information for a document that would initiate PQ documentation. The outline proposes five sections:

1. What is being validated?
2. Why is validation necessary?
3. What else must be done as part of initiating validation?
4. How will validation be accomplished?
5. What else must be done when validation is completed?

Points #1 and #2 above are clear questions requiring a simple answer statement. Direct, clear and concise statements with simple words are recommended to answer these questions. Point #4 describes the actual work of validation that could range from an extensive validation plan to a justification for no work required. Points #3 and #5 should comprise checklists of

associated activities to be initiated early in the validation project and activities expected to be done when validation is completed. These checklists are key documents to integrate the activities of the specific validation within the associated areas of the organization. The above outline may be developed and optimized as appropriate for each organization.

Regarding the respective checklists, multiple versions of the initiation document for specific types of validation and qualification with customized checklists may be developed. These customized checklists could then be more thorough for specific types of validation and qualification and not be overly complex when all activities for all validations are combined. For example, specific checklists may be developed for product / process validation, for cleaning validation, analytical validation, computer validation, equipment qualification, utilities qualification, and so on.

The validation initiation document is a key document. It officially begins the validation. It likely will be the first document to be audited, reviewed, or otherwise consulted when the validation project is in progress. When the “how” component of the initiation, i.e., risk analysis and validation plan, is included in the initiation, it sets the tone for the future execution of the validation. The validation plan leads to subsequent validation documents. Protocols, studies, results, actions, and other work must be consistent with work prescribed in the validation plan. A thorough, complete, and concise validation initiation is key to a successful validation.

Implementation of the concepts described above is accomplished by creating user-friendly templates incorporating the “what, why, how, and what else” format described above. These should be developed by a cross-functional team to encourage widespread support. After the template is created, several model documents describing typical validation projects should be created as examples for future reference. Authors of validation initiation documents will use these model documents as models to help them create new documents. Once the template is officially established, alternate validation initiation formats must not be accepted by the validation function.

Appropriate training is an obvious approach to improving validation initiation documents. Training must be serious, i.e., there must be a commitment to the principles espoused in the training. There are two groups that must be trained on the above concepts. These include validation writers, i.e., those who write validation initiation documents, validation plans, and other validation documents, and the site validation approval committee (VAC), i.e., those who approve the written validation documents. Before this training can start, all must be knowledgeable of validation fundamentals. All involved must be trained in validation basics, terminology, regulations, and other fundamentals.

Application to Quality and Compliance

“PQ Initiation – What, Why, How, and What Else?” addresses sources of variation, omissions, errors, and other undesirable consequences because PQ initiation, a relatively repetitive activity, is not adequately structured. This approach may be adapted to applicable quality and compliance activities. Specific quality and compliance activities including quality systems should be carefully defined to minimize problems. Potential activities to which the above may have application include procedure documentation, stability studies, complaint responses, deviation investigations, non-conformance investigations, CAPA activities, and other quality and compliance activities. This approach should help to structure activities and minimize omissions.

FINAL THOUGHTS

This overview has described problems associated with PQ validation documentation that may have direct or indirect application to quality and compliance documents. Problems and solutions implemented for PQ validation are discussed. The content in this overview was provided by multiple validation managers from numerous pharmaceutical companies in the US and Europe.

The quality of documentation is an extremely important element in the site quality program. While content is of primary importance, document structure, presentation, continuity, grammar, and other non-content elements may have great influence on judgments of the document readers. Quality and compliance investigations must be well designed, clearly written, grammatically correct, and must provide a definite conclusion. All these factors influence the judgments and interpretation by readers including regulatory agency auditors. They further influence perceptions of the associated organizations and individuals. Quality and compliance documents are often among the first documents requested in a regulatory audit – hence their importance in creating initial impressions that may persist throughout an entire audit.

Senior site management and functional management must be openly supportive of good documentation practices in documentation. Employees provide what management wants. Management must be aware of the potential for significant negative consequences of substandard documentation practices. The impressions provided by poorly documented data and sloppy practices may significantly and negatively influence a regulatory auditor. This negative impression may carry over to other areas in the site. Poor practices may even be interpreted as fraud. Site management and functional management must insist on good documentation practices and must show consistent interest in maintaining good practices if sites are to raise their level of performance. Management support must be visible and consistent.

Senior management may not be familiar or have interest in the documentation problems described above. Senior management may focus on financial issues or other non-GMP issues. Quality and compliance personnel may need to persist in educating senior management about documentation problems, and about the potential ramifications of these problems to the entire organization. Efforts to upgrade documentation practices in the organization that require significant changes without senior management support will be futile. If management consistently insists on adherence to good documentation practices, employees will provide good documentation.

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