

Critical Documentation Requirements in Validation-2008 Update

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Editor's comment: "Critical Documentation Requirements in Validation" by Dr. Gamal Amer was originally published in the *Journal of Validation Technology* in 1999. The content of this paper is still valid today. Dr. Amer's discussion provides perspective and insight into the very important topic of documentation associated with the lifecycle approach to process validation. The message of this paper is consistent with recent regulatory publications and presentations that discuss expectations for validated processes, process and equipment understanding, and readily available documentation supporting process validation and equipment qualification.

The equipment, facility, and utilities for the manufacturing, processing, packaging, or holding of a drug product or medical device must be qualified/validated to meet current good manufacturing practice (CGMP) requirements. Thereafter, manufacturing processes conducted in the facility and utilizing the equipment and utilities are validated. Conformance runs are conducted by means of appropriate installation qualification (IQ), operation qualification (OQ), and performance qualification (PQ)/process validation (PV) protocols. These runs are based on prior design and development work that is the basis for the respective equipment/system performance. This work constitutes the equipment and process understanding that is expected for validated processes.

This paper discusses the various documents that describe the work conducted in support of process and

equipment understanding and installation preliminary to qualification and validation. There are five categories of documents addressed in this discussion:

- Engineering design documents
- Operations and maintenance (O&M manuals)
- Construction and installation documents
- Commissioning documents
- Technical support documents for equipment, facilities, utilities, and manufacturing processes.

The above documentation, which describes and characterizes the respective equipment, facilities, utilities, and processes, is used in the preparation of validation protocols; defines the acceptance criteria; and, helps in the preparation of standard operating procedures (SOPs)—all of which are essential to the comprehensive validation effort. Further, these documents will assist in assuring that the equipment and systems remain in the validated state. This discussion is applicable to new installations in which the facility is being built and utilities and equipment are to be installed or received. This discussion is also applicable to existing facilities with installed equipment and utilities. The documents described in this discussion should be accumulated and stored in the validation library where they can be readily available for reference or as requested in an audit.

ENGINEERING DESIGN DOCUMENTS

Based on the fact that validation is confirmatory in nature, the criteria need to be established and confirmed for each system/equipment. Since the manufacture of

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the regulated product of interest requires a properly designed facility and process, the first aspect should be a confirmation that both the facility and the process have been constructed according to design. Therefore, the first set of documents required for the success of the validation effort that need to be collected are all the engineering design documents.

Engineering design documents are the engineering drawings and specifications defining the entire facility, equipment, utilities, processes, and controls. Design drawings can be divided into the following three main categories:

- **Facility design drawings.** These are drawings defining all aspects of the facility itself; for example, architectural drawings define the layout of the rooms within a facility, their sizes, the location of walls and doors, and establish the details for the construction contractor to follow in building the facility itself. Mechanical drawings include drawings defining the design of air handling units (AHU) used in conjunction with the heating ventilation and air conditioning (HVAC) system. These drawings also define the details needed to build and layout the ductwork throughout the facility. Mechanical drawings also include the piping drawings associated with the various water and waste water systems within the new facility. These are known as plumbing drawings.
- **Process design drawings.** These drawings define all aspects of the process operation and include piping and instrumentation diagrams (P&ID). P&ID are drawings that define how pieces of equipment are connected to each other and define sizes and types of pipes used to achieve the connections. In addition, P&IDs define the types of measurements and instruments used to complete such measurements. Isometric drawings are drawings used to demonstrate how process pipes will be installed within the facility in relation to the processing equipment. These drawings are indispensable to the construction contractors when installing the process equipment and defining pipe length and slopes used to insure the sanitary nature of the piping. Control schematics and wiring diagrams define where controllers are installed, how they are wired to each other and to the controller itself. These drawings also define the types of controllers and the input/output logic used to achieve automatic control for the process itself.
- **Engineering specifications.** The engineering specifications for a given piece of equipment will de-

fine characteristics for purchase of the piece of equipment such as material of construction and quality of surface finish; vessel capacity; pressure rating; heating and cooling arrangements and requirements; speeds for motors; and, control requirements. These documents are normally very elaborate and also include commercial terms requirements; specify factory testing requirements to be performed by the buyer; and, enumerate the types of validation support documents required and the number of copies the equipment provider has to supply. Other engineering specifications deal with the general mechanical, plumbing, and electrical specifications. These outline the quality of the materials to be used and the installation requirements for these components. The construction contractor uses these specifications and drawings to bid the projects and define the installation budget and schedule. This information is used during the development of the validation master plan to define many of the acceptance criteria and the entire scope of the project.

OPERATION AND MAINTENANCE (O&M) MANUALS

Validation will eventually demonstrate that once properly installed, a piece of equipment, if operated according to an established SOPs, will produce consistent results over a period of time if, and only if, it is maintained properly and all its critical instruments are calibrated. In addition, preparation of the OQ and PQ protocols require that the protocol define how the equipment is operated in sufficient detail. These requirements suggest a need for a document describing how a piece of equipment is to be operated and maintained as well as what instruments associated with the equipment should be calibrated and how. Such a document is known as the O&M manual and is normally provided by the equipment manufacturer/supplier. When a new project is undertaken, it is customary to have the general contractor purchase the equipment and install it. Therefore, such a document is usually received with the equipment and is filed in the construction office.

The O&M manual provides a considerable amount of information for a specific piece of equipment. This information is indispensable for all aspects of installation, commissioning, operation, and maintenance of the piece of equipment. Following are examples of information that can be found in the O&M manual:

- Mechanical drawings of the piece of equipment
- Installation drawings in detail indicating how to install the piece of equipment
- A procedure to install the equipment
- Model number and other pertinent information for the equipment
- Equipment specifications
- Detailed utility requirements to ensure the proper operation of the equipment
- A replacement parts list with catalog and model numbers
- A recommended preventive maintenance frequency and schedule
- Trouble-shooting procedure
- Detailed procedures for dismantling and maintaining various components
- A recommended procedure to operate the equipment
- A recommended cleaning procedure
- List of recommended supplies to be used in conjunction with the operation and maintenance of the equipment, such as specifications for lubricants, detergent requirements, etc.

If an O&M manual is unavailable for a given system, it becomes rather difficult, if not impossible to successfully prepare validation protocols and other documents required to comply with CGMP requirements. On such occasions, validation and compliance would require the development of an engineering package for the system or piece of equipment. This package will have all available documentation, descriptions of the operation, records of maintenance, sketches representing the various components, and other information related to the operation and maintenance of the system or piece of equipment.

CONSTRUCTION AND INSTALLATION DOCUMENTS

Construction and installation documents are the next set of documents that should be collected. Normally these documents become available during and after the completion of the construction phase. The contractor and subcontractors providing specific services usually develop these documents. Because it is critical when validating a system and/or piece of equipment to be sure that it has been installed correctly and that the drawings used in conjunction with the effort reflect the actual condition, it is important to collect and verify as-built drawings. Purchase orders are nor-

mally used to ensure that the proper equipment has been ordered and that the equipment specifications reflect the original design's intent. Special certifications (certs) are collected and reviewed to ensure that the proper treatment for the system (correct welding, proper testing) has been done. Finally, keep in mind that construction will deviate from the original design no matter how well the facility and process are designed. In order to take all the deviations that may occur into consideration, the validation professional is encouraged to make certain that he/she has access to all construction change orders. These documents are maintained by the construction manager and the design engineer. A review of these documents will indicate what changes have been made to the design; their possible impact on the as-built conditions to be verified during the IQ; and, their impact on the operating acceptance criteria which would be verified during the OQ and PQ phase of the validation.

COMMISSIONING DOCUMENTS

Validation is confirmatory in nature and should not be used in lieu of proper commissioning and start-up. When validation serves as the commissioning and start-up function, failure and deviations from protocol acceptance criteria will result. Organizations choose such an approach believing it will lead to savings in time and money. However, it has been my experience that such an approach saves neither money nor time, but leads to frustration, gives the impression that the validation effort or the design/construction of the facility is lacking, and will inevitably lead to revalidation. Therefore, I strongly recommend that commissioning documents become the next set of documents to be collected prior to executing the validation protocols. These documents will show that the systems are properly operating and have been properly tested prior to conducting the validation itself. In addition, since the contractor normally performs these activities, money and time will be saved if commissioning activities are completed before the systems are released for qualification.

Commissioning documents are normally template forms designed to check for all aspects of the installation and acceptability of a system or equipment. Their objective is to ensure that all components required for operation are in place, operating, and that all connections are made correctly. Their secondary objective is to define 'punch list' items that would require additional work or corrective action by the construction

contractor. Examples of items normally verified in commissioning documents for an HVAC system include motor starter installation and operation; motor rotational direction; secure fastening of detachable components; removal of debris, visual cleanliness of the surrounding area; and, moving parts have been lubricated prior to testing the operation of the system.

TECHNICAL ENGINEERING SUPPORT DOCUMENTS INCLUDING ANALYTICAL METHODS

Finally, in order to complete the validation effort, analytical methods need to be well defined, prove to be reproducible, and accurately reflect the quality characteristics of the material being tested. You also need to calibrate all the critical instruments, either associated with the equipment/system being validated or used to make validation-related measurements. In order to successfully calibrate these instruments, you should have the appropriate calibration procedures. Such documents and procedures that are designed to assist with the validation and ensure that the systems once validated will remain in a validated state (e.g., change control procedure, testing procedures, training records for personnel, calibration certification for the instruments to be used to make measurements during the validation, etc.) are categorized here as technical support documents.

TECHNICAL SUPPORT DOCUMENTS FOR PROCESS VALIDATION

The experimental data, reports, and documents supporting the actual manufacturing process of the pharmaceutical product or medical device are critical for process understanding and are expected to be readily available. These documents may reside in different sites of the company and in areas quite distant from the manufacturing facility. Also, the work they describe may have been done by different organizations. For example, basic science studies may have been conducted by research scientists. Bulk drug laboratory studies may have been done by the organic chemistry group. Product studies may have been done by product research groups. There likely was laboratory scale work, pilot scale work, technology transfer work, and finally trials done using manufacturing equipment at full scale. Much of this work could have been years before manufacturing was initiated, and by personnel who have left the company. These organizations probably have their own document retrieval systems, and these systems probably are unable to be accessed by the validation group. These are signif-

icant challenges in assembling documents that are needed to support the validation effort. There must be agreement, with the product technical support group or technical representative to the process, that these documents are an expectation for manufacturing process validation to be conducted.

OBTAINING DOCUMENTS

Obtaining necessary documents is often a frustrating exercise. Construction contractors usually file documents by trade or purchase order and not by system. For example, all of the drawings representing piping, such as piping drawings for Water for Injection (WFI) systems and piping drawings for the rest rooms in the facility will be filed under plumbing. However, since validation is conducted for individual systems, it is important to have copies of the specific drawing for a given system filed with all the other information for that system. It has been my experience that it is best to assign a validation person as a liaison with the construction contractor. The validation person's efforts should focus on reviewing all information and document packages coming to the construction office and ensure that copies of the appropriate components are filed under the proper system. What I am suggesting here is to have two filing systems to be maintained concurrently:

- Filing system located and controlled by the construction trade
- Validation filing system based on the critical systems and equipment to be validated.

It is also important to realize that construction contractors who are not specifically experienced with building facilities and operations associated with pharmaceuticals or medical devices do not maintain a comprehensive documentation system. Contractors who do not have experience with CGMP installations view document control and collection as a burden. Therefore, you should specify your documentation requirements and the number of copies of each document during the bidding process so that the cost of documentation may be included in the overall cost. I have seen good working relationships seriously damaged because documents were requested too late in the process after the purchase order was issued and the contractor asked for additional money.

When submitting bid requests to contractors or equipment suppliers, make sure you request multiple copies of all the documents you need or think you may need. It seems when it comes to our business, you can

List of Critical Documents Required for Validation

Document Category	Required For	Prepared By	Where Found
<ul style="list-style-type: none"> Design Documents Engineering drawings Specifications 	<ul style="list-style-type: none"> Define systems Define specifications 	<ul style="list-style-type: none"> Engineering organization User groups and operations organization 	<ul style="list-style-type: none"> Construction office or Engineering office
<ul style="list-style-type: none"> Operation and Maintenance (O&M) Manual 	<ul style="list-style-type: none"> Prepare IQ and OQ Prepare SOPs Define preventive maintenance Define calibration 	<ul style="list-style-type: none"> Equipment supplier or manufacturer 	<ul style="list-style-type: none"> General contractor Project manager User files
<ul style="list-style-type: none"> Construction and Installation Documents As built drawings Purchase orders Weld logs Passivation records Change orders Cleaning certificates 	<ul style="list-style-type: none"> Confirm proper procurement or construction Ensure construction changes are recognized. 	<ul style="list-style-type: none"> Construction contractors Subcontractors Equipment installation contractors Trade contractors 	<ul style="list-style-type: none"> General contractor Construction manager
<ul style="list-style-type: none"> Commissioning Documents Test and Balance (TAB*) report Leak test report Filter Test report Commissioning reports 	<ul style="list-style-type: none"> IQ protocol Confirm installation and operation Competent personnel have performed test 	<ul style="list-style-type: none"> Construction contractors Subcontractors Equipment installation contractors 	<ul style="list-style-type: none"> General contractor Construction manager
<ul style="list-style-type: none"> Technical Engineering Documents Analytical methods Change control procedure Test methods Calibration procedures 	<ul style="list-style-type: none"> Analysis of test samples Test specific components Calibrate critical instruments 	<ul style="list-style-type: none"> QA QC laboratory Calibration services 	<ul style="list-style-type: none"> Technical literature Compendium (USP) Library QC laboratory Calibration service
<ul style="list-style-type: none"> Technical Process Documents Laboratory studies R&D reports Product development reports Technology transfer reports 	<ul style="list-style-type: none"> Support manufacturing process Critical process parameters Critical quality attributes Regulatory submission 	<ul style="list-style-type: none"> R&D Product technical support 	<ul style="list-style-type: none"> Technical literature Library R&D Product technical support

*Sometimes called Test Adjust and Balance

never have too many copies of a document. I have actually seen that, by the time you begin production you have lost many of the documents, and in some cases, it becomes impossible to find certain ones. Keep in mind that, normally, equipment suppliers provide the O&M manual with the equipment. However, in order for you to get a jump on preparing your protocols, you could negotiate receiving an advance copy of the manual prior to issuing your purchase order.

DOCUMENTATION LIBRARY

The best way to assure reliable control, access, and retrieval of the documents described above is to file them in a documentation library or document control center. This area should be maintained by a 'librarian' with designated responsibility for document control. There are many documents in a manufacturing facility that must be retained and well controlled (i.e., manufacturing batch records, quality assurance records, de-

viations, and other document associated with manufacturing). The group responsible for storage and control of these records could be requested to maintain and control the validation library. It is essential that the validation library not be freely accessed and documents not be allowed to be removed without accountability. There should be sign-out procedures, follow-up to ensure documents are returned, and associated actions to maintain the integrity of the document collection. Allowing people to borrow documents without accountability guarantees that the library will not be a reliable repository. Documents described in this paper are routinely requested by auditors and must be literally immediately retrieved. Long delays in providing documents to auditors implies a lack of organization and control, both very negative impressions.

TECHNICAL WRITING

An extensive discussion of technical writing is beyond the scope of this paper. However, the following are a few key points to mention that I have found to be very important for the preparation of successful documents:

- **Write for the reader.** Engineers and scientists must realize that they are the individual most familiar with the equipment, facilities, manufacturing process, etc., that they are describing, and that whoever will be reading their document is less familiar with the subject. The reader will probably not have the same educational background as the person writing the document. Although it is impossible to predict who and what background will ever read a specific document, writers must be reminded that the future readers of their documents must be able to understand the information in the document.
- **Documents must "stand alone."** Documents must be written so they would not need additional explanation to be understood. Documents may be requested 10 years after they were originally written, and long after the authors and associated personnel have left the company.
- **Clarity is much more important than brevity.**
- **Rationale and justifications for strategies and approaches must be provided.** For example, why were three samples adequate to describe the process? Why not six samples, 50 samples, even more samples. What is the reason for the acceptance criteria? Why is 50% to 150% of theory an acceptable process?
- **Templates are recommended to provide a common structure between similar documents.** Fur-

ther, they help to minimize omissions. Nothing looks worse than a document that has been amended multiple times to correct mistakes, add information inadvertently omitted, or other changes. These changes imply carelessness and poor planning, all of which are contrary to the confirmatory nature of validation.

- **Results and discussion must be discussed.** It is not adequate to write, "Results pass."
- **There should be a concluding statement.** For example, "The results of this process validation indicated that the manufacturing process is validated." Often documents are well written following the above suggestions, and all testing is acceptable-but the author does not clearly state the important conclusion that the process is validated or the equipment is qualified.
- **Grammar, spelling, sentence structure, and punctuation are important.** Use short and simple sentences. Use small words.

CONCLUSIONS

Document collection is an integral, important, and necessary phase of the validation effort. Having all of the critical documents available or making certain they will be in place by the time they are needed will result in a smooth and successful validation effort. Attempting to short cut or ignoring the document collection step of the validation effort will result in failure of the validation, increased cost of the effort itself, and project delays which would result in lost production.

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