

Validation Master Planning: A Practical Guide for Development

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Validation of a facility and the process used to produce a therapeutic agent is a major undertaking from an effort as well as a financial point of view. As in any complex undertaking, the validation effort represents a complex project requiring coordination and planning. In order to ensure success, an assessment of the resources required and the manpower needed to successfully complete the project should be defined a-priori. The industry standard approach to plan for such a complex endeavor is increasingly through the development of a "Validation Master Plan" (VMP).

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What is a Validation Master Plan (VMP)?

The VMP is a scope document, which is intended to define and enumerate critical systems to be validated and the appropriate approach to validating them. Its main objective is to outline, in sufficient detail, an approach to developing documented evidence that these critical systems consistently perform as designed, in a reproducible fashion and producing a product which meets predetermined quality attributes. This is normally achieved by outlining an approach for managing the size and complexity of the entire validation project, breaking down the entire

operation into subsystems that are treated as separate processes. The entire operation is tested/validated by producing the product and ensuring that all the subsystems function in tandem.

In developing a VMP, the first step of the effort involves defining the critical systems to be validated and the details of the approach to be taken to complete the validation effort. A critical system is a utility or process-related system that may directly or indirectly affect the qual-

ity, safety, and/or efficacy of the therapeutic agent (see *Figure 1*). For example, a Heating, Ventilation, and Air Conditioning (HVAC) system produces air of specific quality and delivers it to a specific production room. An HVAC system is a process as important as the process used for sterile filling of vials and, therefore, would require a process validation step.

To successfully develop the master plan, a project team conducts a series of meetings and discussions to agree on the critical systems for the new process and facility. Normally, such a project team consists of representatives from the following functional areas within the organization: Engineering, Operations, Quality Unit, and Regulatory/Compliance. Inclusion of these functional areas in the development of the master plan ensures their buy-in and gives them a sense of ownership, guaranteeing that the validation effort will proceed smoothly and be completed successfully.

During these initial meetings, the team reviews all engineering and process information in order to define which of the newly installed/constructed systems may have an impact on the quality, safety, and/or efficacy of the product. Once the systems are identified, the performance characteristics need to be extracted from the design specifications, vendor literature, and user requirements. This information is outlined in the VMP and becomes the basis for the general acceptance criteria for these critical systems. In addition, these meetings and discussions will define the standards and procedures to be used to accomplish the objectives of the VMP as well as the various responsibilities for accomplishing such objectives.

What Are The Components of the VMP?

Figure 2 outlines an example of a VMP table of contents. The exact nomenclature for the items outlined in the example will change from one organization to the next. However, the essence of the VMP's content will be the same. It is good practice that any

followed. It is not the final word in validation to be followed to the letter. The approach should indicate the types of protocols to be developed and what they will be used for. It should outline the type of activities to be performed and the sequence for performing them. For example, the approach could suggest that all critical systems will require documented evidence that they have been correctly installed, followed by proof that they are capable of operating at design/required conditions, and consistently producing the product.

The section dedicated to responsibilities will define the responsibilities of the various functional areas within the organization in the execution of the validation effort. This ensures that every responsible department in the organization is aware of its role in the validation effort and the extent of personnel commitment required to meet the objectives of the effort. The section will define who will write, review, approve, execute, analyze the data, and review the acceptance of the protocols. It is strongly recommended that all personnel who will eventually approve the protocols be involved in the develop-

Figure 1.

| Examples of Critical vs. Noncritical Systems | |
|---|---|
| Critical System | Noncritical System |
| USP water producing system | Municipal water system servicing lavatories |
| HVAC system serving production area | HVAC system serving office space |
| Solvent recovery system for reuse in process | Solvent recovery system for environmental protection |
| Compressed air system used for process air | Compressed air for general instrument use |
| Process equipment used in the production of the therapeutic agent | Process equipment used in the production of plant steam |
| Building Automation Systems (BAS) | General electric and lighting system |

strong scope document, such as a VMP, should begin by defining its objective and scope. Such definitions should be short, concise, and to the point. Remember that this is a plan. There will be plenty of time as the validation effort progresses to embellish and use the beauty of the language to its fullest extent.

A brief description, which should be general in nature, of the approach to be used to conduct the validation effort should be outlined. The description should not be restrictive, as it is a plan to be loosely

ment and review of the document. Too many efforts come to a screeching halt because a new group, who had never seen a protocol/document during its development, was asked to approve it. Beware of the disinterest of some stakeholders in the document until they are asked to sign them. At this point, they often suddenly show tremendous interest and raise all types of objections.

A section describing the facility and the process to be validated is normally included in the plan. The description indicates the critical aspects of the opera-

tion, as well as the facility and the rationale for conducting the validation effort. The description should be simple so that the nontechnical management of the organization understands it. However, it should have sufficient technical descriptions so as to allow the staff responsible for implementing the plan to recognize its technical aspects. After all, the validation effort is technical in nature and should reflect that aspect.

Sections identifying the systems to be validated and the protocol requirements, as well as the general acceptance criteria to complete such a validation effort, should also be included as part of the plan. Not every system or piece of equipment requires an Operation Qualification (OQ) and/or a Performance Qualification (PQ). However, all systems/equipment will require an Installation Qualification (IQ) at a minimum. For example, an HVAC system requires IQ, OQ, and PQ while production room finishes, if applicable, would only require an IQ. All of the processing equipment would require an IQ and OQ but not a PQ. Once installation and operation of the process equipment have been verified, the validation of the process itself can proceed, thereby verifying the performance.

Scheduling the validation activities is of utmost importance. Not only does the schedule define when resources will be needed (such as personnel or laboratory support), but it also defines the sequence by which the validation effort is performed. For example, normally validation of a utility-generating system will take place ahead of the validation of a system that will utilize the produced utility. Such critical path analysis is useful in defining the timing for validating the USP water system prior to validating the clean steam generator, which should be validated prior to validating the autoclave using the clean steam. This is a rather important point, since it would be meaningless to demonstrate the consistent performance of a given system without demonstrating in advance that the utilities feeding the system are of consistent quality.

Of additional importance is the use of the overall schedule, which is normally dictated by business consideration in conjunction with the scope of work, to estimate the number of personnel needed to complete the project. Normally, validation protocols are developed by technical writers and engineers, reviewed and approved by Quality Assurance and operations personnel, and executed by technicians under the

supervision of engineers. Using these guidelines, it is possible to estimate the overall cost of completing the validation effort defined in the master plan within the required time frame. Based on such an analysis, the organization could develop an estimate of the cost required to complete a certain validation project and make a decision regarding the use of internal resource versus external consultants to complete the effort.

It is my opinion that the validation master plan should include a section identifying the personnel who will be responsible for the implementation of the plan. In addition, such a section should have some sort of indication as to the criteria for the qualification of those people. Remember that GMP requires that "persons engaged in the manufacture, processing, packaging, or holding of a drug product shall have education, training, and experience or any combination thereof to enable that person to perform the assigned functions" (21CFR211.25, Personnel Qualifications). Therefore, I recommend this section contain the names of the people involved in the project with a short description of their qualifications. This will demonstrate to the regulatory agencies that the proper personnel are working on the project.

The section entitled Supporting Programs normally will list programs that are in place, or to be potentially instituted, in the organization to ensure continued compliance with GMP requirements. It is important to note that GMP is the overall regulation and that validation is only one, albeit a very important, component of GMP compliance. Other programs, such as environmental monitoring, operating procedures, preventive maintenance, and personnel training, should be outlined in this section. Such a section indicates that the organization is well attuned to GMP compliance and supports validation activities with the appropriate programs.

Finally, all examples, drawings, procedures, and other documents supporting the VMP are to be located in the appendices. It is important to include as many example documents and supporting information in the VMP to insure that execution of the validation effort will proceed smoothly.

An effective VMP will be easy to follow, enduring in nature, and will not require too many modifications as the effort progresses. A poor VMP is difficult to follow, unclear in its instruction and approach, ineffectively defines the various responsibilities, is not

clear in defining the sequence of events, and/or results in repetitively invoking the change control procedure. I strongly recommend that the VMP be written in such a fashion that any person with sufficient technical training could follow it and understand what is required to accomplish its objectives.

Getting it Done

The validation master plan is normally developed using a technical writer under the guidance of a senior validation/quality assurance specialist. This specialist, in addition to being very familiar with GMP requirements and validation, must be a strong project manager capable of focusing diverse groups on the task at hand. It has been my experience that the time required for the preparation of a good master plan depends on the complexity of the effort and the number of groups that will eventually be involved in the implementation of the validation effort. Therefore, the cost of developing the plan is very much dependent on these factors and will vary from one project to the next, but will mostly be the cost of the specialist's time since he will be unavailable for other duties during the development of the document.

The VMP is a highly visible and political document. It requires the approval of the organization's management, and therefore, once approved, it insures the buy-in of the policy makers within the organization and allows for the smooth execution of the validation effort. It is important to secure management buy-in by including them in the document's development effort. This can be achieved in various ways:

- ❶ Involve all senior technical managers who will be approving the document in the review process. Incorporate their comments faithfully. If comments are contradictory, attempt to resolve them immediately by having short meetings with the parties involved. Do not wait too long to resolve contradictions; people may forget the rationale behind their comments.
- ❷ Involve the department managers in defining the responsibilities their organization will have to take during the effort. Make sure they agree with the logic of the effort.
- ❸ Conduct frequent meetings to be attended by representatives from the organizations that will be

involved in the effort. Make sure they understand the extent of their department's involvement.

- ❹ Put it in writing and circulate the document in draft form. People can respond to the written word much more effectively than to philosophical discussions. Also, having written drafts shows progress.
- ❺ Make sure the final product (the plan) looks good. Use colors, high quality paper, and pictures if you can. Using today's computers and high quality printers, these documents can look very professional.

As a final note, the worst thing that the developer of a VMP can do is to ask a key person in the organization to approve a plan that he/she never reviewed or participated in its development. This is guaranteed to be the kiss of death for the plan. □

Figure 2

Example Table of Contents for a Validation Master Plan (VMP)

| | |
|------|---|
| 1.0 | Plan Objective |
| 2.0 | Plan Scope |
| 3.0 | Validation Approach |
| 4.0 | Responsibilities |
| 5.0 | Process and Facility Description |
| 6.0 | Systems to be Validated and Protocol Requirements |
| 7.0 | General Acceptance Criteria |
| 8.0 | Validation Schedule |
| 9.0 | Personnel and Their Qualifications |
| 10.0 | Supporting Programs |
| 11.0 | Appendices |

About the Author

Dr. Gamal Amer is the President of Validation and Process Associates, Inc. (VPA). He has over 20 years experience in the pharmaceutical and related industries. He has held senior management positions with leading pharmaceutical and consumer products manufacturing companies. His experience includes comprehensive process design in bulk pharmaceutical chemicals and biotechnology manufacturing as well as pharmaceutical solid dosage manufacturing and containment of potent and radioactive therapeutics. Dr. Amer is well versed in cGMP compliance and validation. He can be reached by phone at 215-657-6070 and by fax at 215-657-6181.