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The Validation Master Plan

How to Write It and How to Make It Work for Your Company

by Norm Howe and Kristi Musgrave

"The second best plan, executed in time, is better than the best plan implemented after the enemy is over the wall" (a Roman General).

That statement is probably even more true today than it was 2,000 years ago. Having a plan, almost any plan, is better than no plan at all. And why is that? Having a plan implies that someone has thought through the consequences of the contemplated activity. It means that at least some contingencies have been considered. Validations can be vastly complex operations. A Validation Master Plan (VMP) drives a structured approach to validation projects that will allow you to address many problems before they become crises.

A VMP is an integral part of an organized validation project. It can be used to document the company's approach to their overall process validation and to organize individual validation projects. A VMP has a broad scope. It clarifies responsibilities, general objectives, procedures to be followed for validation and prioritization of multiple validation tasks. It may reference several protocols to be written in order to conduct the qualification of several different pieces of equipment and different processes. It may also specify schedules for validation and the allocation of resources needed to perform the validation.

Your VMP provides a means of communication to everyone associated with the project. It tells the validation team what they have to do and when they have to do it, and gives them a means of tracking progress. In addition it is a valuable tool when explaining a validation project to an internal or external auditor. An auditor can look at the VMP and realize that the validation project is well thought out and organized; that there is a logical reason for including or excluding every system associated with the validation project based on a risk assessment. A Validation Master Plan can make your project go smoother whether it's a new, greenfield plant, expansion of an existing facility, or a rearrangement of operating equipment.

Developing the Plan

The VMP should be written early in the project. A VMP is a "living document" and will be updated to reflect the most current status of the validation project. A VMP can apply to an entire site. New projects within the site done at a later date can be handled by modifying the existing VMP or by writing a specific one for the new project with reference statements to connect the two plans. Figure one shows a typical table of contents for a Validation Master Plan.

Table 1. Typical Table of Contents for a Validation Master Plan.

1. Approvals
2. Publication Record
3. Responsibilities
4. Introduction
5. Scope
6. Design Description
7. Commissioning & Qualification
8. Computer Systems Validation
9. Cleaning Validation
10. Qualification Matrix
11. List of Required Standard Operating Procedures
12. Equipment & Utility System Descriptions
13. Quality Systems
14. References

Before the design of a new facility you must first decide what you want it to do. How much product do you want to make and what are its critical quality attributes? This is sometimes called the User Requirements Specification (URS). This seems like it might be straightforward, but it usually isn't. The details of the packaging system, specifications, acceptable cost, production capacity, and many others are difficult to nail down.

It is expected that there will be some serious discussion around this point involving marketing, R&D, manufacturing, Quality Control and many other groups. But don't try to bypass this step. You need to get everyone's agreement on the characteristics of the target product up front because this is the point at which validation planning should begin.

The following are descriptions of the essential parts of the VMP:

1. The **Approvals** section contains the signatures and job titles of the people who author and approve the Validation Master Plan
2. The **Publication Record** contains the revision history of the VMP. The VMP is meant to be a working document. That is, it changes to reflect the changing

reality of a rapidly moving facility with many projects or even just a few. As the Roman General implied, if we wait until we can perfect our plan, the market will pass us by and there will be no need for the project. Therefore we have to plan for change and be ready to change the plan.

3. The **Responsibilities** section defines who is responsible for what.

4. The **Introduction** specifies the company, business unit, and location. It gives an overview of the business and explains why the project is being implemented. This section will also detail the types of products that are produced at the facility along with the type of system that is used (Aseptic filling, Fermentation etc…). In this section the author may focus on how the new process or equipment will add to the overall quality of the facility.

5. The **Scope** defines the limits of the validation project and details which equipment is included in the project and which is not.

6. In the **Design Description** you briefly, but systematically, describe the design of the new installation or process. In the case of a new process in existing equipment enumerate the critical process parameters and tell how they affect product quality. With new equipment or facilities the design description will include physical characteristics such as size or volume, and descriptions of supporting utilities or materials of construction. Here is where one should explain how the design of the installation enhances quality, such as cleanability of surfaces, room classifications and isolation barriers. Particular mention should be made of how flow patterns of people, materials and equipment were taken into consideration during the design to minimize contamination of the product.

7. **Commissioning & Qualification**. In this section you should assess the risk posed by a failure in each plant system and provide a rationale for why the system is validated or not. If a system has no significant impact on the quality of the product then you may decide that normal commissioning is sufficient. In other words that the installation has been verified and documented to comply with the applicable Good Engineering Practices (GEP). GEP's may refer to industry standards such as the American Society of Mechanical Engineers (ASME), the American National Standards Institute (ANSI), or the National Electrical Manufacturers Association (NEMA) among others.
   The first pass Piping and Instrument Diagrams (P&ID's) are a good place to define system boundaries and begin the Risk Assessment process. The risk assessment is made based on three criteria: severity of the outcome in case of a failure, probability of a failure, and detectability or warning properties of the failure. The FDA wants to know why a system was excluded from validation as well as why it was included. Declare the type of validation you are performing (retrospective, concurrent or prospective) and why. Describe in this section the format that will be followed while writing protocols and include references to sources for the format whether they are company protocols or literature. Don't forget to include the sampling plan in the protocols for process validation.

8. **Computer System Validation**. Provide the rationale for validating or not validating each computer system that affects the quality of the product. For instance, does it store quality critical data?

9. The centerpiece of the VMP is the **Qualification Matrix**. It serves as a reference point for all of your validation activities. In this section you should list in tabular form all of the utility and process systems associated with the project. Indicate which protocols will be written for each system (see Figure 1). The Risk Assessment, which was done in the Commissioning and Qualification section defines how the X's are to be distributed on the Qualification Matrix. In keeping with the utility of the VMP as a communication tool, the Qualification Matrix can be used to track the progress of the validation project once the VMP has been approved.

10. **List of Required Standard Operating Procedures**. This section is also composed in tabular form and can also serve as a tracking mechanism for the progress of the project.

11. The **Equipment and Utility System Descriptions** briefly outline the purpose and operational concept of each system. In addition you should think through at this time what qualification tests you will conduct and consider how you will determine acceptance criteria.

12. **Quality Systems**. Once the new process is validated the FDA wants to know how you intend to keep it in a validated state until the last batch of product is produced. The VMP demonstrates how you intend to accomplish that by laying out the list of SOP's that support the validated systems. Listed below are some of the procedures that you should have:

    - **12.1. Corrective And Preventive Action (CAPA).** When an error occurs in your process, you need to find the root cause and install a solution that will prevent the error from happening again.
    - **12.2. Preventive maintenance/calibration.** A procedure, which explains how equipment will be maintained and calibrated. It should contain clear instructions on what to do when the as-found condition of equipment is outside the acceptable limits.

12.3. **Training.** You must have a procedure that details how you will insure that your personnel have the training, experience and ongoing education required to staff your plant.

12.4. **Change Control.** This procedure or procedure guides personnel through the steps necessary when a change occurs in either the design of the project, documentation, equipment or procedures. Management may decide to institute separate procedures to cover each of these different types of change. Revalidation may be incorporated into these documents or it may become a separate document; particularly if you will revalidate on a set schedule regardless of whether there have been any known changes in the process.

12.5. **Out Of Specification results (OOS).** You must have a clear procedure for handling OOS results that includes a determination of whether there was a clear, assignable laboratory cause for the anomalous result.

12.6. **Deviations.** Deviations occur in the workplace, whether it is planned or not. However, any deviations that occur in the manufacturing or testing of a bulk or drug product must be documented and corrective action must be taken.

12.7. **Failure Investigations** are performed to document the investigations and resulting actions involving a known off-specification batch or Customer Complaint. Due to the compliance scrutiny that failure investigations must endure, these investigations must be thorough and complete.

12.8. **Audits** are the process by which all other quality systems and personnel behaviors are assessed for effectiveness. You should have a procedure which details how audits are to be conducted and what will happen as a result of each audit.

13.

References. List all state and federal regulation, company policies, and engineering standards which apply.

Description	Com	IQ	OQ	PQ	CSV	Other
Equipment and Control Systems						
Ultrasonic Washer 600	X	X	X	X	X	Cleaning
Cryogenic Freeze Dryer 1000	X	X	X	X	X	Cleaning
Filling Line with Isolator 101	X	X	X	X	X	Cleaning
Autoclave 610	X	X	X	X	NA	Cleaning
Formulation System DCS Modules	X	X	X	X	X	NA
Building Management System	X	X	X	X	X	NA
Utilities						
Fire Water System	X	NA	NA	NA	NA	NA
HVAC	X	X	X	X	NA	NA
DEMIN Water	X	X	X	NA	NA	NA
Nitrogen	X	X	X	NA	NA	NA
Plant Steam	X	X	X	NA	NA	NA
Compressed Air	X	X	X	NA	NA	NA

Key:
Com - Commisioning
IQ - Installation Qualification
OQ - Operational Qualification
PQ - Performance Qualification
CSV - Computer System Validation
NA - Not Applicable

Figure 1. Example of a Qualification Matrix

Conclusion

Your finished Validation Master Plan will tie together all protocols necessary to complete the validation project. The VMP should clearly communicate the company's intent to start production using the new process or equipment in a fully compliant state. The VMP approval process is not just an exercise in bureaucracy. The approval process insures management understanding of the scope of the effort and buy-in before the work starts. The VMP can also provide invaluable information into resource planning activities and cost estimation. It can provide the basis for competitive bids for outside contract help as well.

Although the VMP serves many uses after it has been compiled, perhaps its most useful function accrues while it is being written. It provides a structured process whereby the project can be thought through in advance and problems can be detected and resolved

prior to executing the individual protocols.

References

1. Federal Food, Drug and cosmetic Act, Chapter III, Sections 301, 3, 4, as amended by the FDA Modernization Act of 1997.
2. US Food and Drug Administration, 21 CFR parts 210 and 211.
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4. ISPE Baseline@ Pharmaceutical Engineering Guide: Pharmaceutical Engineering Guides for New and Renovated Facilities; Volume 3, Sterile Manufacturing Facilities, first Edition, January 1999, pages 119-120.

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