

This article describes the elemental requirements of a Validation Master Plan (VMP), what it should look like, what level of detail should be included, and FDA expectations.

Reprinted from
PHARMACEUTICAL ENGINEERING®

The Official Journal of ISPE
May/June, 2001 Vol. 21 No. 3

Reasons, Regulations, and Rules: A Guide to the Validation Master Plan (VMP)

by Brian W. Saxton

The US Food and Drug Administration (FDA) has been explicit in the need for validation, but implicit on the elements of that program. The chanting of the “thou shalt validate” mantra is heard throughout the Drug, Biologics, and Medical Devices sections of the Code of Federal Regulations (CFR), but, alas, there is no boilerplate template to follow. Organizations are thus left to interpret the regulatory requirements and craft individual programs to comply. Is there a guiding principle that can be applied here, to help companies distill reams of mind-numbing regulations into elemental validation requirements?

An adage about public speaking says there are three keys to a successful presentation:

1. Tell them what you’re going to say.
2. Say it.
3. Tell them what you said.

This adage, in a slightly modified form, can be used to describe the major elements of a Validation Program:

1. Tell them what you’re going to do.
2. Do it.
3. Tell them what you did.

This three-step outline is a greatly simplified model of the multitude of tasks associated with a validation program, but is an accurate summary of the goals of each step of the process. The role of the Validation Master Plan is to help an organization “get its arms around” a project-specific validation effort by setting the scope by which all subsequent documents shall be bounded.

To see how the parts of the validation program fit into this modified adage, let’s briefly review the elements. “Validation Program” is

an umbrella term, encompassing all of the components below - *Table A*.

Validation Master Plan (VMP)

The VMP serves as the validation roadmap, setting the course, justifying the strategy, outlining the preliminary test and acceptance criteria, and documenting the necessary programs that ensure a continuing state of validation.

Qualification

The Qualification phase provides documentation that equipment and utility systems were installed properly through an Installation Qualification (IQ), operate correctly through an Operational Qualification (OQ), and perform effectively through a Performance Qualification (PQ). Qualification assures that the criteria set forth in the Basis of Design documents generated at project inception have been met in the field installation.

Process Validation

Building on the data generated from the Qualification phase, the Process Validation (PV) phase focuses on the reproducibility of the systems used and the resulting product quality. This program challenges the ability of the systems used (methods, equipment, and operators) to meet the pre-approved design intent.

Final Reports

Final Reports (FR) compare the conclusions of data gathered to the acceptance criteria outlined in the Qualification and Validation phases. They determine the pass/fail status and address the resolution of any deviations. They also can be referred to as Summary Reports.

Compliance Programs

The Validation program must ensure policies and procedures comply with current Good Manufacturing Practices (cGMP). Systems such as calibration, preventative maintenance, change control, and revalidation contribute to a continuous state of validation.

Validation Program	
Validation Master Plan (VMP)	Documents Intent and Pathway
Qualification (IQ/OQ/PQ)	Confirms Design Intent
Process Validation (PV)	Assures Process Consistency
Final Reports (FR)	Summarizes Test Results vs. Acceptance Criteria
Compliance Programs	Ensures Continuing State of Validation

Table A. Validation program.

Considering the above, we can now complete the Validation Program adage:

1. Tell them what you're going to do (VMP).
2. Do it (IQ/OQ/PQ/PV).
3. Tell them what you did (FR).

This article will focus on the "Tell them what you're going to do" part of the Validation Program, otherwise known as the Validation Master Plan.

Planning Overview

The purpose of the VMP, in a prospective or concurrent validation effort, is to explain the validation rationale associated with the installation, start-up, and use of a new production line. This rationale should review manufacturing systems and assess the potential of each to affect end-product quality. The new process may be as simple as an accessory change on existing product equipment, or as complex as a new building with all new utilities and equipment. The size and scope of the project determines the size and scope of the resulting VMP. For a retrospective validation effort, the VMP documents the existing production line and outlines the anticipated test and analytical methodologies to be employed.

The VMP should be authored for its audience, including the organization's quality, engineering, and regulatory departments, the FDA, and potential outside contractors. Each group looks for different elements. Outside contractors want a Deliverables List on which to base quotes and define the scope of work; the FDA looks for the pre-approved intention to comply with Federal regulations; while in-house quality, engineering, and regulatory departments look for an accurate representation of systems and corporate policies. The VMP should address all of these concerns.

The VMP serves the purpose of documenting the intent of the validation program, and therefore needs to be pre-approved by the same departments that will ultimately be responsible for reviewing and approving the subsequent protocols. At a minimum, this includes Regulatory Affairs, Quality, and Engineering.

Opening a Dialogue with the FDA

There are a number of good reasons to create a VMP: the FDA's expectation that one be created, determining resource scheduling and loading, and defining the necessity to create or amend corporate procedures. However, one function of the

VMP is often underutilized: serving as a vehicle to open up dialogue between the regional District Office of the FDA and the organization. Initiating a pre-submission meeting with the FDA to review the VMP will save time to market by addressing any concerns about the validation philosophy or methodology up front, when the correction of those issues is not on a critical path for time to market. This allows companies to work with the FDA in an advisory versus an enforcement mode, which will help take some of the anxiety out of the validation process and improves its chances of success. The FDA's Center for Biologics Evaluation and Research (CBER) has published a document through its "Manual of Standard Operating Procedures and Policies" that discusses this. It suggests that a "brief description of the validation procedures including the validation master plan"¹ be submitted for review prior to the "pre-NDA" (New Drug Application) meeting. Although this procedure was written for Biologics, the benefits of such meetings for Drug and Medical Device products is obvious, particularly if there are unique processing steps and/or equipment that the average FDA compliance officer may not be familiar with.

Regulatory References to Validation and Planning

The FDA can determine prohibited acts and penalize drug and device manufacturers who market adulterated product.² An adulterated product is one whose quality characteristics can not be satisfactorily assured due to nonconformity with current Good Manufacturing Practices (cGMPs)³. The definition of "adulterated product" is straightforward, but preventing its occurrence can be complex. In essence, a Validation Program ensures that systems, policies, and procedures exist to prevent the manufacturing of adulterated products. It's in the cGMPs for Drugs (21CFR 210 & 211), Biologics (21CFR 600) and Devices (21CFR 800) where the need for validation is specified.

Drug Products

For drug products, Parts 210 and 211 of the cGMPs refer loosely to maintaining "appropriate validation data." However, the practice of validation is implied more strongly in § 211.68 (a): "Automatic, mechanical, or electronic equipment or other types of equipment, including computers, or related

Typical VMP Contents	
1.	Introduction
2.	Scope
3.	Facility Description
4.	Commissioning
5.	Qualification
6.	Process Validation
7.	Computer System Validation
8.	List of Required Protocols and Procedures
9.	List of Required Standard Operating Procedures
10.	Equipment and Utility System Descriptions
11.	Computer System Description
12.	Other cGMP Programs
13.	References

Table B. Typical VMP contents.

Process Equipment/Other Systems

EQUIPMENT	Comm.	IQ	OQ	PQ	PV
Reactor System Series 100	✓	✓	✓	✓	✓
Centrifuge	✓	✓	✓	✓	✓
Catch Tank	✓				
Solvent Storage and Distribution	✓	✓	✓	✓	✓
Glass Lined Mix Tank and TCU	✓	✓	✓	✓	✓

Utility Systems

UTILITY SYSTEM	Comm.	IQ	OQ	PQ	PV
Fire Water System	✓				
Breathing Air System	✓				
Cold Glycol System	✓				
USP Water System	✓	✓	✓	✓	✓
HVAC	✓	✓	✓	✓	✓

Legend

- Comm.: Commissioning
- IQ: Installation Qualification
- OQ: Operational Qualification
- PQ: Performance Qualification
- PV: Process Validation
- Not Applicable

Table C. List of required protocols and procedures.

systems that will perform a function satisfactorily, may be used in the manufacture, processing, packing, and holding of a drug product.” The burden of proof lies with the manufacturer to show equipment will “perform a function satisfactorily,” and that proof should take the form of in-process testing or alternately, Process Validation.

To clarify the validation requirements implicit in this regulation, the Agency issued a Federal Register Notice proposing changes to Parts 210 and 211.⁴ One change would offer this definition: “Validation protocol means a written plan describing the process to be validated, including production equipment, and how validation will be conducted...”⁵ Another proposed section states: “The manufacturer’s determination of equipment suitability shall include testing to verify that the equipment is capable of operating satisfactorily within the operating limits required by the process.”⁶ In both of these cases, a well-crafted VMP will show the Agency the pre-approved intent to comply with the expectations of cGMP regulations.

Biologics

For Biologics, Part 600 addresses unique considerations associated with biological products and blood components. Biological-derived drug products must adhere to Parts 210 & 211. Also, cGMP section § 601.12 requires validation for changes to an approved application. “Before distributing a product made using a change, an applicant shall demonstrate through appropriate validation... the lack of adverse effect of the change on the identity, strength, quality, purity, or potency of the product...”⁷ This requirement governs changes in “...product, production process, quality controls, equipment, facilities, responsible personnel, or labeling...”⁸ Whether the change is

major or minor, a VMP will provide the Agency the basic components of the organizational validation philosophy and intentions to comply with applicable regulations.

Medical Devices

For Medical Devices, 21 CFR 820 serves as the cGMP requirements section. Section 820.75 deals with Process Validation and states that the “validation activities and results, ... and where appropriate the major equipment validated, shall be documented.”⁹ This outlines the need for a validation program, and the VMP can help comply with this requirement by documenting which major equipment systems will be validated.

Part II

All regulated industries are struggling to understand and comply with the requirements of 21CFR 11, which addresses Electronic Records and Electronic Signatures, and requires “Validation of systems to ensure accuracy, reliability, consistent intended performance, and the ability to discern invalid or altered records.”¹⁰ Based on the number and complexity of the computer systems utilized, a separate Computer System Validation Master Plan may need to be written and referenced in the VMP. Here again, this can serve as a vehicle for a pre-execution meeting with the FDA in order to gain guidance.

These specific instances do not explicitly detail the requirement for a Validation Master Plan; however, a properly crafted VMP will document the pathway to compliance.

VMP References

Increasingly, the FDA is showing it agrees. Recently, the Agency issued a “Guidance for Industry” document, meant to



...address the selection criteria governing what equipment and utility systems need to undergo Process Validation.



reflect the Agency's current thinking, that explicitly calls out for a VMP. In "Guidance on Quality System Regulation Information for Various Pre-Market Submissions," a requirement of the Quality System Manufacturing Dossier is "a copy of the Validation Master Plan or a description of which manufacturing processes have been or will be validated. A Validation Master Plan is a convenient method of quality planning for process validations required in the manufacturing of the device (§ 820.20(d))."¹¹ Clearly the expectation of the Agency is that organizations have a validation strategy as part of product and process development, and translate that strategy into a plan that will lead to an installation compliant with regulatory requirements.

The Validation Master Plan

Listed below are the headings for the major sections of a VMP followed by a description of the purpose and the suggested content - *Table B*.

1. Introduction

This section should include the company name, location, division or subsidiary name (if applicable) and business sector served. A short overview of the project provides the reader with the necessary background from a macro standpoint. A cross-reference to the relevant company Quality Assurance Policy is appropriate here.

2. Scope

This section defines the breadth and reach of the validation effort covered by the VMP. A brief description of the installation, whether single- or multi-product, and a breakdown of installed equipment as new or existing should be included here.

3. Facility Description

Whether the project is a new building, extension, or remodeling of a current building, the facility characteristics are listed here. The number of floors, the inter-connectivity of process and utility systems, isolation means, and the design product and personnel flow used to minimize cross-contamination are identified. Be sure to note any room classification (cleanroom certification levels) and specialty surfaces and finishes integral to achieving the required product quality. Process Flow Diagrams (PFDs) are useful here, depicting the anticipated personnel, raw material, process, and waste material flow. The emphasis here is on design considerations to eliminate cross-contamination of material.

4. Commissioning

Document here the selection criteria governing what equipment and utility systems will undergo Commissioning. As Commissioning is not part of the Validation Program and is not regulated by the FDA, people often wonder why they should include this section at all. The reason is the FDA is just as interested in the rationale behind why one system is not

validated while another is. The VMP needs to answer that question, identifying support utilities that do not need to be validated because they do not directly affect product quality. It also demonstrates thoroughness, showing the FDA that all systems have been examined for product quality impact. To maximize the usefulness of commissioning, the system should be tested within the anticipated operating range of the respective OQ.

5. Qualification

The selection criteria governing what equipment and utility systems will undergo Qualification is discussed here. Individual definitions of IQ, OQ, and PQ, may be included. Company policies, regulatory references, and published guidelines used in this selection process should be addressed. This discussion may include considerations such as product contacting surfaces, critical/non-critical instrumentation, direct and indirect systems,¹² and downstream processing, among others. A discussion of protocol and final report formats may be included here, with either a reference to existing protocol development procedures, or a description of the format to be utilized. Final Reports may be generated as attachments to the protocols themselves, or as separate documents.

6. Process Validation

This section addresses the selection criteria governing what equipment and utility systems need to undergo Process Validation. Company policies, regulatory references, and published guidelines utilized in the selection process should be addressed. One such criteria is if the "results of a process cannot be fully verified by subsequent inspection and test, the process shall be validated..."¹³ Also included is a discussion on the appropriate Cleaning Validations (CV) required to verify inter- and intra-campaign cleaning methods. *If this is to be a finished product, Packaging and Sterility validation needs to be addressed.*

7. Computer System Validation

A separate section should be devoted to the discussion of Computer Validation, whether that is in the form of a Programmable Logic Controller (PLC) or a Distributed Control System (DCS). Computer Validation criteria also should be discussed, and whether the installed control system is to be 21 CFR 11 compliant, i.e., secure audit trails, authority checks, etc.

8. List of Required Protocols and Procedures

Include here a tabular representation of the equipment and utility systems, and the required protocols and procedures associated with each - *Table C*. This is the essence of the VMP because it defines the validation requirements for the project, and can be used to determine resource loading. This table can subsequently be used as a "Deliverables List" if the validation effort is contracted outside of the organization.

9. List of Required Standard Operating Procedures (SOPs)

This should take the form of a tabular representation of the installed equipment and utility systems and the required SOP associated with each, similar to the List of Required Protocols and Procedures. This will help identify the level of SOP generation necessary to complete validation activities. These will generally take the form of Operation, Maintenance, and Cleaning SOPs.

10. Equipment and Utility System Descriptions

An overview of the particular system should be given, aligned with the Basis of Design documentation. Table D serves as an example of specific verbiage used in a typical VMP. A listing of proposed Qualification tests (IQ/OQ/PQ) should be identified with a brief description of the procedure and how the associated Acceptance Criteria will be determined. As the VMP should be developed early in the planning stage, many system specifics will be in the draft phase and subject to change. To avoid duplication of effort and unnecessary revisions, do not assign numeric-specific Acceptance Criteria in the VMP. Those details will be fully delineated in the respective Qualification

“

With the inclusion of some additional information ... the VMP can help serve as a resource- and task-planning tool

”

and Validation protocols that will follow. Keep in mind the intent of the VMP as a scope and guidance document. System-specific acceptance criteria fall under the auspices of the individual protocols.

Section 10.0: Equipment and Utility System Descriptions

Nitrogen Distribution System

Description

Nitrogen gas is distributed throughout the facility using a network of carbon steel (from supply to inline filter) and stainless steel (from inline filter to use point) piping. Nitrogen gas is obtained from an existing 400-psig nitrogen gas system located in the facility.

A one-micron filter is utilized to filter high-pressure nitrogen to be used in the Series 100 Reactor System for pressuring, purging, and for the agitator gland seal. Nitrogen line pressure from the header is reduced prior to use-point delivery. Low-pressure header branches service the tank farm and production areas, and each branch will utilize a one-micron filter, as well as upstream and downstream pressure indicators to verify filter cartridge integrity.

Installation Qualification

Installation Qualification will be performed in accordance with the guidelines specified in SOP #95IQ001. All IQ data will be documented in an approved Installation Qualification protocol – Protocol preparation, review, and approval will be scheduled to coincide with the installation of the Nitrogen Distribution System.

Operational Qualification

Operational Qualification of the Nitrogen Distribution System will be performed in accordance with the guidelines specified in SOP #95OQ001. Proposed OQ testing and the corresponding acceptance criteria are described below.

System Capacity Testing/Flow Determination

Under maximum use conditions (system design basis), nitrogen flow rate and system header pressure must remain acceptable.

Static Pressure Testing

Nitrogen pressure at usepoints must meet system specifications and end user requirements.

Performance Qualification

Performance Qualification of the Nitrogen Distribution System will be performed in accordance with the guidelines specified in SOP #95PQ001. Proposed PQ testing and the corresponding acceptance criteria are described below.

Moisture/Dewpoint Determination

The measured dewpoint at selected usepoints must closely correspond to the dewpoint of the supply.

Particulate

Particulate measurements will be at or below predetermined levels.

Oxygen Concentration

Oxygen concentration at predetermined usepoints must closely correspond to the oxygen concentration of the supply.

11. Additional cGMP Programs

The VMP is meant to be a Validation Life Cycle document. It should cover the activities and requirements from project inception to testing completion and on through a program of continuous monitoring and evaluation. Associated with this effort are Quality Assurance/Quality Control procedures meant to support and update the validation effort. These programs include, but are not limited to:

11.1 Document/Change Control

A procedure must be in place to govern and capture documentation creation, revision, and control. This procedure will be applicable to all validation documentation, and must designate the review and approval responsibilities of various functional groups. Archival guidelines shall include duration of record retention, and means of storage and retrieval.

11.2 Standard Operating Procedures

SOPs shall exist to address such cGMP issues as facility sanitation, waste collection and disposal, the use of suitable rodenticides, insecticides, fungicides and fumigating agents, and building maintenance.

11.3 Calibration

A system shall exist detailing the methods, frequency, and documentation of the calibration program including justification for a “no calibration required” status.

11.4 Preventative Maintenance

This system will be indexed to distinct equipment identifiers, and outline the maintenance procedures required to ensure proper system functionality. This procedure will identify the appropriate documentation and frequency requirements.

11.5 Revalidation

A crucial part of the Validation program is determining when to revalidate. This determination may be periodic, or triggered by the replacement of critical instruments. Part of the Change Control program will be an assessment of the impact of any proposed change on the validated state of the affected equipment, and if revalidation is required.

11.6 Operator Training

A program must exist to ensure and document that personnel shall have the appropriate education, training, and/or experience to perform their assigned functions. Personnel shall be trained on good sanitation practices, as well as the use of protective apparel to prevent product contamination.

Table D. Example of an equipment and utility system description.

12. References

All company policies and procedures, as well as any applicable local, state and federal regulations, and industry standards referenced should be listed.

Input to the VMP

A certain minimum level of documentation needs to be developed in order to produce a VMP. An equipment list, which provides basic specifications such as size/capacity, instrumentation and controls, design/operating limits, and capabilities needs to be available. Additional documentation such as a "Design Basis" is important to delineate how equipment and utility systems should perform, independently and in concert, to produce the product. For Biologics and Pharmaceuticals, generally a set of preliminary Piping and Instrumentation Diagrams (P&IDs) helps define system boundaries. For Medical Devices, the Manufacturing Flow Diagrams required in the Manufacturing Dossier section of the Pre-Market Submission also may provide system boundary information.

Approval of the VMP prior to the generation of the associated protocols is as important as approval of protocols prior to data collection. Just as protocols require QA approval prior to execution, the VMP requires QA approval prior to protocol generation. The VMP should be under revision control, as it documents corporate approval of the scope and intent of the validation program, and will require QA approval. Any Basis of Design or validation philosophy changes should be pre-approved in the VMP prior to the generation of the affected protocols. The VMP needs to be updated to document major project scope changes such as the addition or deletion of equipment, and project completion (i.e., release to production). This provides a clean audit trail of pre-approved intent versus execution.

Conclusion

In its simplest form, the VMP is meant to document the major equipment and utility systems associated with the production process, assess the impact on the quality of the resulting product, and determine the validation requirements. With the inclusion of some additional information; however, the VMP can help serve as a resource- and task-planning tool. For instance, a Deliverables List can be developed from the "List of Protocols," which can be used to gauge the man-hour requirements of the job, for either internal budgeting or comparing outside contractor quotes. The "Additional cGMP Programs" section can isolate the need for policies or procedures to be created and/or updated.

The creation of a VMP at the beginning of the project serves many purposes: to identify the timing and level of anticipated resource needs, to document the corporation's validation philosophy and individual elements, and to show the FDA the pre-approved intent to bring on a new product line in full compliance. It is well worth the extra time spent to write this document at project inception, and to get early regulatory feedback via a pre-submission meeting with the FDA, than to answer Agency questions during the approval cycle and pay with a delayed product launch date.

References

1. U.S. Food and Drug Administration, Manual of Standard Operating Procedures and Policies, Communication, SOPP 8101.1, Version 1, Effectivity date February 11, 1999.

2. Federal Food, Drug and Cosmetic Act, Chapter III, Sections 301, 303, 304, as amended by the FDA Modernization Act of 1997.
3. Federal Food, Drug and Cosmetic Act, Chapter V, Section 501 (a)(2)(B), as amended by the FDA Modernization Act of 1997.
4. U.S. Food and Drug Administration, 21 CFR parts 210 & 211, Proposed Rule, Federal Register, Friday May 3 1996 Docket No. 95N-0362.
5. U.S. Food and Drug Administration, 21 CFR parts 210 & 211, Proposed Rule, Federal Register, Friday May 3, 1996 Docket No. 95N-0362, page 20113, proposed § 210.3 (b) (23).
6. U.S. Food and Drug Administration, 21 CFR parts 210 & 211, Proposed Rule, Federal Register, Friday May 3, 1996 Docket No. 95N-0362, page 20115, proposed § 211.220 (c).
7. U.S. Food and Drug Administration, 21 CFR 601.12 (a), April 1, 2000.
8. IBID
9. U.S. Food and Drug Administration, 21 CFR 820.75 (a), April 1, 2000.
10. U.S. Food and Drug Administration, 21 CFR 11.10 (a), April 1, 2000.
11. U.S. Food and Drug Administration, "Guidance for Industry and/or for FDA Staff: Guidance on Quality System Regulation Information for Various PreMarket Submissions," Draft Guidance-Not for Implementation, Draft released for comment on August 3, 1999, Section 19. Design History File (DHF).
12. 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.
13. U.S. Food and Drug Administration, 21 CFR 820.75 (a), April 1, 2000.

About the Author

Brian W. Saxton is the Manager of Validation Services at Process Facilities Inc. in Boston, MA. He is responsible for client-based validation programs including master planning, protocol generation and execution, and final reporting. He has been involved in developing and executing validation programs for the past 12 years for various regulated industries. He has a BS in chemical engineering from Manhattan College, Bronx, New York, and an MBA from Boston University, Boston, MA.

Process Facilities Inc., 160 Federal St., Boston MA 02110.
bsaxton@processfacilities.com. 