Validation Master Plans—
Reader Q&A

Alyson Stevans and Justin Pawlik

“Validation Strategy and Planning” discusses various topics associated with validation master plans that are useful to practitioners in validation and compliance. We intend this column to be a resource for daily work applications. The key objective for this column: Usefulness.

Reader comments, questions, and suggestions are needed to help us fulfill our objective for this column. Manuscripts or case studies submitted by readers illustrating validation strategy and planning are also most welcome. Please send your comments and suggestions to column coordinator Stephen Perry at stephen.perry@kymanox.com or to coordinating editor Susan Haingey at shaingey@advanstar.com.

“Validation Strategy and Planning” previously published three articles on various components of validation master plans (VMPs). “Validation Master Plans—Defining a Quality System,” published in the Journal of Validation Technology (JVT), Volume 14, #5 (Autumn 2008), discusses the overall strategy and content of a VMP including planning, policies, and commitments. Further, the strategy and content of the VMP reflects the attitude of the organization toward validation.

“Planning Aspects of Validation Master Plans,” published in JVT Volume 15, #1 (Winter 2009), focuses on systems inventory, schedule, and lifecycle management. Prioritization of validation work depends on the potential risk of each system to patient and product.

“Validation Master Plans as Commitment Documents,” published in JVT Volume 15, #2 (Spring 2009), discusses the various aspects of commitment including management commitment, how compliance will be achieved, and plans for validation including ongoing maintenance of the validated state.

These articles have prompted specific questions from our readers. This issue’s installment responds to questions submitted by readers requesting more detailed and specific information. The authors welcome additional questions or topics for discussion and will address these in future columns.

QUESTION #1. OUR COMPANY DOES NOT HAVE A VMP. WHAT IS THE FIRST THING WE SHOULD DO?

Although a validation master plan is not formally required by the Code of Federal Regulations (CFR), it is often one of the first items an inspector will request to see when auditing a company. The VMP is a useful tool for documenting how the validation program within the company or facility is managed (1). The first thing a company should do is define its validation policy, as this will help structure the VMP. The validation policy should define the organization’s scope of validation including which systems will be validated and the respective validation boundaries.

If possible, a VMP should be written prior to the initiation of validation activities because it is an important planning and commitment tool. However, because a VMP is not a requirement, companies do have the option of proceeding with their validation efforts without having first written a VMP. Each of these situations will be discussed below in more detail.

Creating a VMP “from scratch” may seem like a formidable task. To alleviate this difficulty, it is recommended that the VMP be broken down into separate key components. The three main sections of the VMP should be the following:

- Systems inventory
- Validation schedule
- Validation lifecycle management.

Each of these topics contains specific aspects of a com-

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plete validation. First, the systems inventory includes every system and the respective components of each. Additionally, the systems inventory indicates which of these components need to be validated, including the required level of validation for each. Second, the validation schedule provides a logical timeline of the validation, including the order in which the systems should be validated. Naturally, some validations must occur before others, and including these dependencies will assist with structuring the schedule. For example, a process validation protocol cannot be executed until all of the equipment validations are completed. Finally, validation lifecycle management includes a plan for maintaining the validated state of the system, as well as the post-validation activities to monitor the performance of the system. The latter is consistent with the 2008 FDA draft process validation guidance for pharmaceuticals (2) and with 21 CFR 820.75(b) which states that it is required to establish and maintain procedures for monitoring and controlling process parameters in validated processes (3). An example of post-validation monitoring is the creation and approval of annual environmental monitoring reports for validated cleanrooms.

Throughout the process of creating a VMP, it is helpful to refer to the various governing regulations that each system will have to meet. It is also important to establish how the validation will be carried out and reference the procedures and protocols that will be written to meet the requirements of the VMP.

For the situation where a company has already started or completed validation without a VMP, it is still recommended to write a VMP. This retrospective VMP should essentially be a formal summary of what has been validated and how the validation was performed. This information can be captured in the systems inventory and validation schedule as described previously. It may also be necessary to formulate the validation lifecycle management plans, including post validation activities, if they have not already been implemented. These plans should also be incorporated into the VMP. Time spent on this retrospective work pays big dividends when FDA asks to see the VMP. Hopefully, a company makes all future VMPs prospective in nature.

**QUESTION #2. MUST THE VMP CONTAIN ALL PIECES OF EQUIPMENT, ALL PARTS, ETC.?**

The systems inventory organizes all of the equipment, processes, computer systems, etc. into a well-categorized, easy-to-understand, and logical list. The systems inventory also captures the validation requirements for each item. Therefore, it is recommended that all components of each system are included in the VMP. This communicates that all components have been considered when planning validation and nothing has been overlooked.

Within the complete systems list, explain the function of each component, specify whether or not it requires validation, and define what level of validation is necessary (e.g., installation qualification [IQ], operational qualification [OQ], performance qualification [PQ], method validation [MV], process validation [PV], cleaning validation [CV], and computer system validation [CSV]). The different types of qualification are outlined in ICH Q7, Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients (4) and Annex 15 to the EU Guide to Good Manufacturing Practice (5). The required level of validation should be determined from the regulatory guidelines already outlined in the VMP. Additionally, a formal risk analysis can be performed to support any decisions. Additionally, the rationale for any decision to not validate a specific component or system is just as important and needs to be documented in the VMP. A qualification matrix is a useful tool for organizing and conveying this information. Refer to Figure 1 for an example of a qualification matrix.

The author of the VMP may also choose to utilize boundary drawings. These are not a necessary part of the VMP but they help to define the scope of a system and are an easy way to see what is included and what is not included.

Some companies prefer to assign asset numbers to minor components of major equipment. For example, a mixing tank, mixer impeller, motor, control system, and transfer piping may each have an individual equipment number, even though the entire system is always used as a unit and has been validated as a unit. In this case, only the major unit (mixing tank) should be noted in the VMP. However, all individual piece equipment numbers should be listed in the IQ/OQ/PQ for the system. Also listed in the IQ/OQ/PQ would be alternate identical backup components for which the validation would be applicable. The combined VMP and individual validation documentation (IQ/OQ/PQ) would then provide accountability for all major equipment, systems, and associated parts.

**QUESTION #3. WHO SHOULD BE IN CHARGE OF THE VMP?**

A VMP should be coordinated and managed by the group that is responsible for all other validation activities at the company or facility; normally, this is the validation department. Although the validation department may be responsible for the VMP, it is crucial that all groups impacted by the validation activities, including the quality,
manufacturing, and regulatory departments, are involved with the development, approval, and maintenance of the VMP. Most importantly, VMP authorship should be delegated to a single individual to ensure the document is well written. This designated author may contribute very little to the overall content if the document is prepared by other contributing authors.

**QUESTION #4. HOW OFTEN SHOULD THE VMP BE UPDATED?**

Each organization should decide on an individual basis how often the VMP must be updated. Some organizations perform annual reviews of the VMP. Other organizations prefer more frequent updates, such as a quarterly review and update. A validation review includes an evaluation of all validations performed since the most recent approval of the VMP. A review of current validation policies (i.e., company policies and regulatory policies) should also be performed. Based on the review, the VMP should be updated to include any new systems or policies. In addition, if a new component or system requires a different type of validation that was not previously outlined in the VMP, the new type of validation should be added.

The number and frequency of audits (e.g., external, internal, regulatory, client, etc.) may help the organization to determine the frequency of review and update. An organization that has frequent audits may find that using an annual review and then discussing post-review activities and providing individual reports is more cumbersome than performing more frequent updates (i.e., maintaining the VMP in an essentially continuously updated state).

It should be noted, however, that it is not always necessary to update the VMP to accommodate new components or systems. The systems inventory can be made an attachment to the VMP so updates to the VMP are not required if any new equipment is added. The VMP would not require updates as long as the new systems follow the same validation approach as previous systems.

Another method for organizing VMPs, which may help to avoid major revisions, is to use a nested hierarchical system. This nested hierarchy utilizes three tiers of VMPs: global, site, and process VMPs. In the event that a process related change is made, it is possible that the change will only affect VMPs at the process level, leaving the global and site VMPs unchanged.

**QUESTION #5. SHOULD THERE BE ONE VMP OR SHOULD THERE BE A COLLECTION OF SMALLER VMPS SUCH AS PRODUCT AND PROCESS VMP, CLEANING VMP, COMPUTER VMP, ETC.?**

The decision to have one all-encompassing VMP or multiple VMPs should be made on a company-by-company basis. One deciding factor for the number of VMPs may be the size of the company or facility. Larger companies may see value in reducing document contents and overall length by using a nested hierarchy of VMPs, which consists of global, site, and process VMPs.

The global VMP defines the overarching company policies and outlines the organization’s method for meeting regulatory requirements. According to ICH Q7, Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients, the global VMP states the company's overall policy, intentions, and approach to validation (4). The site VMP allows each site to interpret the rules listed in the global VMP. It also includes the systems inventory, validation schedule, and validation life-cycle management plan. The process VMP is the most detailed VMP and is applicable to a specific process at a given site. It defines the system's complete validation. Utilizing this nested hierarchy of VMPs provides different layers of context for the VMPs, and allows each VMP to be more concise, specific, and directly relevant. Refer to Figure 2 for a possible hierarchy structure of VMPs.

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**Figure 1:** Example qualification matrix in a VMP (1).

<table>
<thead>
<tr>
<th>#</th>
<th>System</th>
<th>IQ</th>
<th>OQ</th>
<th>PQ</th>
<th>MQ</th>
<th>PV</th>
<th>CV</th>
<th>CSV</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Filling Machine</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>2</td>
<td>Capping Machine</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>3</td>
<td>Cleaning Machine</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>4</td>
<td>Empty Bottle Detection</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>5</td>
<td>Product Manufacturing</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>6</td>
<td>Equipment Cleaning Process</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>N</td>
</tr>
</tbody>
</table>

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**Figure 2:** Possible hierarchy structure of VMPs (1).

For smaller companies, with fewer systems, facilities, and policies, it may be more useful to have just one VMP that functions as the global, site, and process VMP. It is possible to include the overarching company policy, validation schedule, protocol references, and more, in just one document without losing the usefulness of the VMP.

**QUESTION #6. HOW DOES RISK ANALYSIS IMPACT THE VMP?**

Risk analysis can be used to justify the chosen level of validation for a given system or system component. Risk analysis should examine the potential impacts on the process and resulting product. The guidelines detailed in ICH Q9, Quality Risk Management (6) and GHTF Implementation of Risk Management Principles and Activities within a Quality Management System (7) provide information on utilizing a risk-based approach to determine the necessary level of validation for a given system. The primary factors that should be considered are the overall safety and efficacy of the product from the perspective of the patient. Additional factors include the impact on critical product attributes and critical processing parameters.

For example, a custom computer program can be validated using black-box testing, rather than more rigorous code structure testing, if the resulting outputs of the computer program are not critical and can be verified elsewhere in the manufacturing process. A risk assessment can be performed to show that the limited black-box testing approach is adequate when taking into consideration the overall process.

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**REFERENCES**

**ARTICLE ACRONYM LISTING**
- **CFR** Code of Federal Regulations
- **CSV** Computer System Validation
- **CV** Cleaning Validation
- **EU** European Union
- **GHTF** Global Harmonization Task Force
- **ICH** International Conference on Harmonisation
- **IQ** Installation Qualification
- **MV** Method Validation
- **OQ** Operational Qualification
- **PQ** Performance Qualification
- **PV** Process Validation
- **VMP** Validation Master Plan