

A robust validation approach designed specifically for device manufacturers

The United States Food and Drug Administration (FDA) defines “validation” as “establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes”¹.

The skills required to validate a new piece of equipment or process undeniably add value to the commercial proposition of a delivery device manufacturing business. Without the necessary validation skills, manufacturers needing to introduce a new process or piece of equipment face delays, additional costs and ultimately dissatisfied customers. Conversely, the right skills and approach will deliver efficiencies, which not only serve to improve time and cost to market but also strengthen the relationship between the manufacturer and its customer.

Validation within a specialty medical device manufacturing environment is an essential part of Good Manufacturing Practice (GMP) which in itself is a key element of any Quality Assurance process. In fact, in today’s world, validation competencies are expected by pharmaceutical partners and indeed form a larger part of the manufacturing solution as there is a growing demand for products and services to satisfy ever increasing levels of scrutiny.

We all expect the products and services we buy to perform to a certain standard and the role of validation is to ensure the parameters, which influence that standard, are all controlled. In a highly regulated environment such as device manufacture there is an obvious need to ensure that both process and product deliver what is expected. Depending on the application, a process validation can affect the end product considerably as the accuracy of the drug delivery system is a vital element in the efficacy of the final drug therapy.

¹ Guideline on General Principles of Process Validation May, 1987

It should be noted that validation is the responsibility of all departments associated with the design and manufacture of products or services and should not be the sole responsibility of the Quality Department. Indeed, the process of validation is largely an engineering responsibility, though the organisation as a whole has to decide for itself what is required. A note of caution: the objective of validation must be kept firmly in mind at all times as without regular review validation exercises may grow disproportionately.

Don't dive into validation until you're sure you understand the process

Before any new validation, a number of questions may need to be answered as a means of establishing a protocol for the Operational Qualification (OQ) of the new process. This is the point where other techniques can be accessed in a preliminary step e.g. a design of experiment.

A case in point would be Bepak's current elastomer project. In this example, Bepak has undertaken several 'design of experiments'² in order to establish the significant process parameters for each process step. Once understood, the process can be tested for responses to these significant parameters. Once the optimum process is identified then "stability" or "robustness" runs can be used to verify that the process is in control; these runs should include different input material batches (ideally at least three for each input material) to generate as much variability as would reasonably be expected during routine production. Once the process step is stable then it can be linked to other process steps to create a 'rolled up' process validation. The resulting process outputs (materials or components) can then be used in final product testing (product PQ).

It is critically important that the process is understood before you undertake process validation otherwise unforeseen problems may emerge. A failure to understand the process at this early stage will inevitably lead to continuous improvement activities in the post-production stage.

The initial OQ stage is critical to the final production process and the resulting quality of the materials or components. The message here is clear - investing time at the OQ stage will yield benefits later.

² A Design of Experiment (DOE) is a structured, organised method for determining the relationship between factors (X) affecting a process and the output of that process (Y).

Validation is not just about reducing cost; there are other benefits too

Imagine a piece of equipment (perhaps several years old) has to be moved to a different location (a common scenario in these days of consolidation). The equipment produces an end-product that may require extensive testing and there may be business drivers to release product at risk (pending final test results). How is the decision to release product made?

A re-run of the IQ and PQ after the equipment has been moved provides a valuable quantitative (measurable) basis upon which to resume production using the equipment. Along with other quality characteristics, this may well provide the confidence to re-start production *before* any results are available from final product testing.

Using this approach effectively reduces the risk of failure later. Moreover, whether final testing exists or not, without such an approach on what basis does one re-start production? Manufacturers should satisfy themselves that they have taken all reasonable steps to quantify that the product from the equipment satisfies the original acceptance criteria and if not, understand why. The adage '*listen to the process*' is appropriate in this context.

The following paragraphs define the overall validation process and have been drawn from several sources.

Master Validation Plan (MVP) - A formally approved plan documenting the critical and non-critical areas for validation. A MVP is needed for each project undertaken. The plan should include the purpose and scope of the validation, user requirements in general, responsibilities, documentation required, plant and equipment to be validated or a rationale if a certain validation is not required. The MVP is the roadmap for the validation.

The Validation Steps

Installation Qualification (IQ) is established by delivering objective evidence to show all key aspects of the process, equipment and ancillary system installation adhere to the manufacturer's approved specification, and that the recommendations of the equipment supplier are suitably considered.

The principal features of each installation should be documented and sufficient information must be available to allow the equipment to be operated and maintained effectively, safely and consistently.

Operational Qualification (OQ) establishes objective evidence of process control limits and action levels which result in a product that meets all predetermined requirements.

Performance Qualification (PQ) establishes objective evidence that the process, under anticipated conditions, consistently produces a product that meets all predetermined requirements.

Performance Qualification is normally carried out on a minimum of three runs and should use the conditions (generated as a result of the OQ stage) that have been approved for the process. All product produced must meet its previously determined specifications and the validation run batch sizes must be representative of the batch sizes manufactured during normal operations.

IQ, OQ and PQ relate to the three levels of specifications that can be described as follows:

-

Requirements Specification describes what the equipment or system should do. In a process context, this is written by the medical device manufacturer, or in the case of a product validation, by the IP owner. Requirements specifications should always be written in conjunction with the pharmaceutical partner. This links to the Performance Qualification that is used to test such requirements.

Functional Specification is usually authored by the supplier and describes the detailed functions of the equipment or system (i.e. what the system will do). This links to the Operational Qualification that tests all the functions specified.

Design Specification is a complete definition of the equipment or system in sufficient detail to enable it to be built. This links to the Installation Qualification, which checks that the correct equipment or system is supplied, that it meets the required standards, and that it is installed correctly.

The illustration below summarises the main steps reviewed in this article.

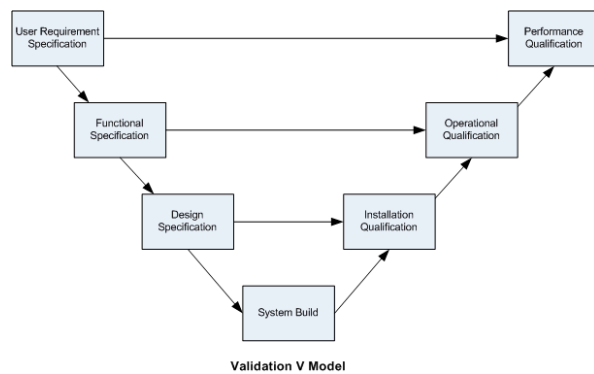


Figure 1 (overall validation steps)

A great deal of detail is required to support a good validation method. It must be remembered that the process should be logical and straightforward and, if successfully completed, it will add value.

Other validation steps that may be considered in a medical device manufacturing environment are as follows: -

Technical Specification Qualification (TSQ) A formal document that records that an item purchased 'off the shelf' meets the TRS.

Factory Acceptance Trials³ (FAT) Tests conducted at the supplier's premises as part of the validation process. These tests are used to prove the operating efficiency of the machine and to ensure that any problems are resolved prior to the equipment being shipped for installation and commissioning.

Planning validation activities

³ Strictly speaking a FAT is not a validation requirement, however many organisations see this step as an important equipment milestone to which commercial elements can be applied. A FAT is the first real test of a new piece of equipment. In addition to FAT, the use of SAT (Site Acceptance Testing) can also be considered which is, in fact, a straight repeat of the FAT except that it takes place on the client's premises. Both these steps will have their own protocol (and report) with acceptance criteria important to the client included.

A validation protocol must be written for each stage of the validation process prior to commencement of the validation activity. The protocol must include:

- Aim
- Scope
- Responsibilities
- Method
- Acceptance Criteria

The protocol is a key document; the protocol content (what is to be validated, or to be more specific, *what is it* about this process or piece of equipment that is important and that could affect the final product) is the key understanding to a successful validation activity.

Recording the outcomes of validation

Validation Report A written record of the validation process containing the objective evidence that the validation has been undertaken according to the validation protocol and that the results meet the documented acceptance criteria. The Validation Report will include the following sections: -

- Summary
- Aim
- Method
- Results
- Conclusions

The language used in this article may vary depending on the organisation; however the overall objectives of each step should be closely aligned with the methodology described.

Conclusion

In order for a medical device manufacturer to be considered a credible partner by a pharmaceutical company, they must be able to demonstrate robustness in their validation approach. As an essential part of Good Manufacturing Practice and any valid Quality Assurance process, it is a critical element of the overall offer. In addition, when delivered well it can add real value to the business both in terms of cost reduction and time saving.

There are a number of important considerations for a new validation process; be clear about the objective and purpose of the validation; involve the relevant parties, particularly the Quality and Engineering departments; above all else, understand the process, test the outcomes and create a review protocol to ensure that the process is kept on track.