VALIDATION: SIGNIFICANCE OF A DOCUMENTED DEVELOPMENT STAGE IN PROCESS VALIDATION

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ABSTRACT

Quality is always an imperative pre-requisite when we consider any product. Drugs must be manufactured to the highest quality levels. End product testing itself does not guarantee the quality of the product. Quality assurance techniques must be used to build the quality into the product at every step and not just tested for at the end. In pharmaceutical industry, Process Validation performs this task to build the quality into the product because it is a proven fact for quality management of pharmaceuticals. The trends in Pharmaceutical Quality Assurance changed when FDA (Federal Drug Administration) of USA published new guidelines on Process Validation in 2011. The above guideline introduced the lifecycle approach of process validation. The details, some of them are compared with the European regulations. The typical changes in the pharmaceutical practice of drug manufacture from earlier time till today have been highlighted.

Keywords: Process Validation, Good Manufacturing Practice, Transformation, FDA, Critical factors, Quality Risk Analysis.

INTRODUCTION

The process validation is standardization of the validation documents that must be submitted with the submission file for marketing authorization.¹ The process validation is intended to assist manufacturers in understanding quality management system (QMS) requirements concerning process validation and has general applicability to manufacturing process.² Process Validation is defined as the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality products.

Pharmaceutical production essentially has to meet the two basic requirements:

a) Fulfill the expectations of the customer that is “customer satisfaction”.

b) Secondly to meet the GMP regulations which have the force of law.

GMP as we call it Good Manufacturing Practice are a set of regulations or activities that protect the customer from purchasing a product that is not effective and can prove dangerous. Thus the pharmaceutical companies have to take proactive steps to make sure
that their products are pure, effective and essentially meet the desired standards. GMP regulations require a quality approach to manufacturing, enabling companies to minimize or eliminate cases of contamination, mix ups, or any other errors. GMP regulations are often mentioned as “current”, i.e. “cGMP” expresses that manufacturers must employ technologies and systems which are up-to-date to comply with the regulations.

**TRANSFORMATION: FOR IMPROVED QUALITY**

The pharmaceutical industry has been going through a remarkable transformation to keep a pace with technical evolution and competitive environment. Inclusion of both chemical and technological aspects, strategic business considerations has made the concept of quality rather complex. These conditions forced pharma producers, for instance, to elaborate customer-oriented strategies in order to know how to fulfill needs and expectancies, and to handle complaints in a proper manner.

The information technology has led to the development of suitable softwares that have helped in making data collection, its handling and reviewing it faster and easier. Further these software packages have helped in obtaining a properly designed process for the efficient use of resources by the management and therefore improving the working atmosphere of the enterprise, for e.g.,the well known SAP (System, Application, Product in Data Processing), and specifically the quality module of the software that can be operated in accordance with the cGMP regulation. This has enabled the companies to analyse the company data and plan a strategy for their business. For instance, logistics of the process, qualification of the supplier and quality control of the incoming raw material can be integrated into the computer system. The pharma industries have to maintain quality and this is possible when they learn from their past bad experience if any. The quality can thus be improved by introducing different systems, the well-known CAPA system (Corrective Action and Preventive Action), under which the handling of process deviations, out-of-specification results, observations of self-inspections and of external audits etc can be coordinated for example is one such system.

The interaction between the technical-informational background of pharma firms and the customers or authorities has led to the development of more effective and sophisticated tools. The company requirements are also harder and very often the approach of a given
process also becomes more complex. The publication of the new FDA guidance (FDA, 2011) fits into this progress. The publication of the new FDA guidance (FDA, 2011) fits into this progress.

**LATEST TRENDS IN VALIDATION ACTIVITIES**

According to the corresponding ICH (International Conference on Harmonization) guide “process validation (PV) is the documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce an intermediate or API meeting its predetermined specifications and quality attributes”. However, in 2011 the FDA guidance states that “process validation is defined as the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product”. Moving further the latest definition is the one already mentioned in the introductory part.

The new trend divides the activity into three stages:

**Stage 1: Process Design**

The main focus is exclusively on qualification efforts without also understanding the manufacturing process which is defined during this stage based on knowledge gained through development and scale up activities. It covers all activities relating to product research and development, formulation pilot batch studies, scale up studies, transfer of technology to commercial scale batches, establishing stability conditions and storage, handling of in process and finished dosage forms, equipment qualification, installation qualification, master production document, operational qualification and process capacity. This is the stage in which establishment of a strategy for process control is taking place.

**Stage 2: Process Qualification**

This is the process validation phase. It is designed to verify that all established limits of the critical process parameters are valid and that satisfactory products can be produced even under the worst conditions. It includes the performance of three consecutive runs at the intended commercial scale. The manufacturing process qualification is performed under a prospective protocol using the appropriate output and results from the stage 1 studies (i.e. critical process parameters), in process controls and specifications, and any additional criteria specific to the process. During this stage, the process design is
evaluated to determine if the process is capable of reproducible commercial manufacturing. GMP procedures must be followed in this stage and successful completion of this stage is necessary before commercial distribution of a product.

Stage 3: **Continued Process Verification**

It is the assurance of that the production process remains in the state of control during the entire period of the routine production. It is known as the validation maintenance Phase, it requires frequent review of all process related documents, including validation of audit reports, to assure that there have been no changes, deviations failures and modifications to the production process and that all standard operating procedures (SOP’s) include change control procedures, have been followed. The ongoing assessment of process performance through life cycle qualification and management of process changes.

Critical process parameters are monitored routinely during batch release. After validation, all changes made to manufacturing procedures are assessed for impact to the validated process and revalidation is performed as needed.

While earlier, FDA emphasized on the results, testing, documentation and the protocol for validation, the new trend that is according to the 2011 approach, the need for validation starts in the development stage itself further continuing through out the life cycle of the product. The batches to be run for the validation process is decided accordingly. Normally three consecutive production batches are run and hence a comparison is made is made between the results of the three batches.

There are some points to be kept in mind as follows:\textsuperscript{10}

1) The use of different lots of components should be included, i.e. API’s and major excipients.
2) Batches should be run in succession and on different days and shifts (the latter condition, if appropriate).
3) Batches should be manufactured in equipment and facilities designated for eventual commercial production.
4) Critical process variables should be set within their operating ranges and should not exceed their upper and lower control limits during process operation. Output responses should be well within finished product specifications.
5) Failure to meet the requirements of the validation protocol with respect to process inputs and output control should be subjected to requalification following a thorough analysis of process data and formal review by the CMC Coordination Committee.

The expectation of ICH is similar: “For prospective and concurrent validations, three consecutive successful production batches should be used as a guide, but there may be situations where additional process runs are warranted to prove consistency of the process (e.g. complex API processes or API processes with prolonged completion times).” After declaring the process validated in the Process Validation report, the validation activity is finished according to the “old” concept.  

Since Process Validation is part of the integrated requirements of a quality management system, it should be conducted in the context of a system including design and development control, quality assurance, process control and corrective and preventive action. The product should be designed robustly to withstand variations in the manufacturing process. The manufacturing process should be capable and stable to assure continued safe products that perform adequately. Each corrective action applied to a manufacturing process should include the consideration for conducting process validation.

It was also stated in 1987 by the FDA: “This guideline is issued under Section 10.90 (21 CFR 10.90) and is applicable to the manufacture of pharmaceuticals and medical devices. It states principles and practices of general applicability that are not legal requirements but are acceptable to the FDA.”

In-process and finished-product inspection or testing cannot assure quality. The process conformity should be demonstrated and the maintenance of the validated, controlled state of the production should be integrated into a single complex aspect. It is in this light that the producer should carefully monitor each manufacturing step to consistently assure that the finished product meet all quality attributes as specified. Moreover ICH has allowed: “As an alternative to the traditional process validation, the continuous process verification can be utilized in process validation protocols for the initial commercial production and for manufacturing process changes for the continual improvement throughout the remainder of the product lifecycle.
IMPROVEMENT IN THE VALIDATION ACTIVITIES AS A PART OF DEVELOPMENT

Knowledge is must and forms the basis for manufacturing a process, a controlled Strategy has to be looked for. Not only this the Process Validation approach should be such that it leads to continuous improvement. The development in the pharmaceutical field for which process validation is of utmost importance is a major requirement of cGMP regulation for finished pharmaceutical products. The quality goals are successfully met with if the process is validated. Successful validation not only leads to improved quality but it also reduces the dependence upon the in process and finished product testing.

According the FDA’s view on Process Validation(FDA, 2011) it is understood that Stage 1 is generally described as “process understanding”. Understanding of all the process parameters and determining which parameters are critical. Evaluation of the process parameters and their ranges are a part of pre-qualification activities. A process pre-qualification plan based on a well defined manufacturing process is key to meaningful pre-qualification studies. Each parameter is assessed for its potential to affect (positively or negatively) the applicable process controls or quality attributes.

A fundamental step to Process Validation is to recognize the critical steps and parameters of the production process that influence product quality.

Some of the critical factors which affect conducting effective process validation are listed below:

1) The quality system (infrastructure) should support the validation effort by way of documented control, calibration, preventive maintenance, etc.
2) All the critical points of the process should be clearly identified.
3) The process should run using the extremes of the system at the critical points (worst case).
4) Adequate run (data) are required to provide statistical support to demonstrate product consistency.
5) The execution of the protocol should follow the requirements of the validation document, where all deviations form the validation document well recorded and followed up properly.
6) Before approving validation the area should be conformed for the requirement of validation.

These factors are important for the manufacture to understand and detect the occurring variations. The sources, presence, degree, impact of variations should be identified and suitable control should be established. The early process design was not conducted under cGMP but now the decisions and justification of controls are made in the form of review documents.

Thus ICH issued “A New Vision for Ensuring Product Quality” that addressed a “harmonized pharmaceutical quality system applicable across the life cycle of the product emphasizing an integrated approach to quality risk management and science”. In the above approach also the (transferred) knowledge forms the basis for the manufacturing process, control strategy, Process Validation approach and ongoing continual improvement.

QUALITY RISK ANALYSIS

Since it is not possible to test everything, it is necessary to pick a subset of the overall set of tests to be run. Quality Risk Analysis can help one focus the test effort. Since it is not possible to test everything, it is necessary to pick a subset of the overall set of tests to be run. Quality risks analysis can help one focus the test effort.

Following are five techniques for analyzing risk:

Informal quality risk analysis techniques do not entail much beyond what is described in this section so far. Such techniques provide an easy way to get started in quality risk analysis. One is likely to miss some important areas of risk, especially during early risk analyses, but even informal techniques make it possible to achieve a better degree of test focus and coverage than one can achieve without any risk analysis at all.

For ISO 9126 quality risks analysis techniques, one should use the quality characteristics and sub characteristics described in the ISO 9126 system quality standard as the categories for the risk analysis. The six main characteristics of quality are functionality, reliability, usability, efficiency, maintainability, portability.

Cost of exposure quality risk analysis techniques focus on the following question: What are the expected losses associated with various risks, and how much should one spend to reduce those risks? An expected loss is the product of the probability of the loss
multiplied by the cost of the loss. Such techniques allow the project management team to make a hard-nosed, economic decision about testing.

**Failure mode and effect analysis** goes beyond discussing risks. Using this technique, the risk analysis team tries to identify the different ways the system could fail and all the possible effects those failures would have on customers, clients, the business, society, and so forth. This technique is quite detailed. It can produce finely calibrated testing, but it also can produce a ton of paperwork and lots of invested time.

**Hazard analysis** techniques are like failure mode and effect analysis, but done backward. One starts first with the effects—the hazards—and tries to work backward to causes. Along the way, the likelihood of those causes should become clear. In some cases, though, there are many causes of different kinds of bad behaviour, so this technique tends to work best with systems that do only a few things.

While the phrase quality risk analysis may sound forbidding, mystifying, and complex, the underlying ideas—and the techniques—need not be. Simply put, quality risk analysis is a process for identifying, analyzing, and prioritizing categories of potential quality problems (that is, bugs) in one’s systems.\(^1^4\) The R&D delivers the data for risk analysis in the form of detailed development reports. Quality Risk Analysis is the key of establishing critical process parameters on true scientific basis. The areas where particular focus is to be made and where the data needs to be demonstrated for high level of assurance of commercial process robustness can be done by conducting risk assessment prior to release of commercial validation batches. For this to be successful, co-operation between R&D and production department is crucial. Hiyama (and many other authors) pointed out, “for innovative PV approaches, technology development and senior management support are required”.\(^1^5\)

It is must to keep in mind that the degree of control over attributes or parameters should correspond with their risk to the process and process output that is to say, attributes or parameters posing higher risk, higher degree of control is appropriate.

The new FDA guide issued in 2011 states that “the terms attributes (e.g. quality, product, component) and parameters (e.g. process, operating, equipment) are not categorized with respect to criticality”. The reason for this statement is explained by the next sentence “the perception of criticality as a continuum rather than a binary state is more useful”, since
risk based decisions are expected throughout the lifecycle of Process Validation. All attributes and parameters should be evaluated in terms of their roles in the process and impact on the product or in-process material, and re-evaluated every time when new information becomes available. This proves that the final and the ultimate goal of Process Validation is still homogeneity within a batch and consistency between batches.

CONCLUSIONS

Process validation is an essential requirement of pharmaceutical industry for finished pharmaceutical products. Validation is a tool of quality assurance which provides confirmation of the quality in equivalent systems, in process, software and testing methods. Validation of individual steps of the manufacturing process is called process validation. A properly designed system will provide a high degree of assurance that every step, process change has been properly evaluated before its implementation. Three consecutive batches are taken up for process validation. Re-establishment of the strategy of quality management is often done with the changing attitude of regulations and authorities. This fact can lead to the recasting and rethinking of the organizational structure of quality assurance. Even the re-allocation of human resources may become necessary. Right from the stage of design, the quality has to be built into the product. This proves the importance of archived documents or the development reports. The reports right from the development stage till the end of manufacturing process be it old or new have to be kept intact. Development experiences have to be properly documented and handled as an extremely important source of knowledge in solving further technological problems since it creates the scientific justification and knowledge source of every further activity in and for production.

REFERENCES

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