Validation

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India, China and Turkey are the fastest growing Pharmaceutical markets and overall the E7 (Largest emerging economies) will see their markets grow at a CAGR of 11.5 percent between 2007 and 2012 to a value of 11.6 bn, compared with 4.95 percent for the G7 economies. Markets for drug substance and drug products in India, China, Russia and Indonesia are dominated by generic products. There is less penetration in Brazil, Mexico and Turkey with generics, IPR and counterfeiting still remain significant issues in the E7 (source: RNCOS).

A new culture of low cost sourcing for Pharmaceutical equipments purely depend upon the manufacturers, the days of pharmaceutical companies buying the best technology available with all the features is slow downed. Total cost of ownership (TCO) is one of the major factors in purchasing decisions. In the past, lines packing patented drug products would often run at no more than 50 -60 percent capacities, as the value of the product meant costs were not a critical factor. Today all the resources are expected to sweat so machine flexibility, quick changeover, clean ability and efficiency are most important.

India has rapidly increasing pharmaceutical machinery sector boasting about 800 companies. This sketch outs more than four million people and exports USD 6 bn of its drugs annually. Steadily and gradually Indian machineries are taken up to the international standard requirements and the problems rolled out to sites outside India considerably rectified and controlled, a price/ performance ratio improved by modular design and customized service packages.

The mass of pharmaceutical products available further complicates the cost pressure equation. For e.g. short runs i.e. fours or two pack and many batches are often a few hundreds or thousands. The challenge of min and max batch size issues for customized orders. This can present enormous issues as companies must clean and validate the machine for each product. Many a times that some machine companies merely pay lip service to validation and are more interested in the process than the integrity of the machine. **The quality of the product and integrity of the equipment should go hand in hand.**

One of the concepts is validation; most of the major machine suppliers do a good job in this area and have designed machines which can be cleaned, changed and ready for use both efficiently and effectively. There is no point in making a machine ready in an hour's time if the documentation practice takes more than an hour or so. Further there should be less room for compromise on quality for processing machines. The process has to be 100 percent accurate and verifiable. Therefore Equipment qualifications play an important role from manufacturing point of view as well as Machine suppliers to meet Regulatory Requirements.

A thinking of performing systematic inspection has worked and possibly termed as *'Drug in- process inspection and validation'*. The proof of validation is obtained through the collection and evaluation of data, preferably beginning from the *process development phase and continuing through in to the product phase*. Validation necessarily includes *process qualification such as materials, equipment, system, building and personnel, but it also includes the control of the entire process for repeated batches or runs.*

Carrying out validation is not only a Regulatory requirement, but also makes sure a sense from engineering as well as a business point of view. It is evident that pharmaceutical companies that are well versed in conducting process validation have a competitive advantage over those who are not.

The equipment qualification is done with the cooperation between Technical team and Manufacturing team. If the equipment qualification is not carried out then it will be history or exception, at times it will lead to retrospective qualification, many use the risk analysis method i.e. failure mode and effects analysis or carrying out requalification after major modifications or carrying out requalification regularly after two years. Therefore it is necessary to carry out equipment qualification as per definitions and their benefits are as follows:

Equipment qualification

Definitions: Installation qualification (IQ), Operational qualification (OQ), Performance qualification (PQ),

Benefits:

- # Provides the evidence needed to satisfy the requirements of Regulatory / Quality Agencies.
- # Equipments are qualified as per set protocols and ensured that the equipments perform according to the specifications.
- # Decrease the risk of financial loss caused by non compliances and provide uniform documentation from industry to industry worldwide.
- # Ensure confidence in the integrity of their measurements, with traceable documentation that given them, their customers and Regulatory Agencies a complete record.
- # Trained and certified service engineers perform the procedures.

Regulatory Requirments For Validation

Quality is always an essential prerequisite requirement when we consider any Product. It becomes most important tool when it relates to any *Life Saving Products in Health sector / Pharmaceuticals.* In today's requirements, quality has to be built into the product right from its inception and rigorous international environmental , efficacy, safety and Regulatory standards.

It is compulsory for the Agency and from the Regulatory point of view that ,Quality of a Product is just not enough satisfactorily controlled solely by carrying out by compendial method of analysis provided by Pharmacopoeia for the Final drug product, it is necessary the product should be proven stable indicating according to set of Regulatory guidelines / GMP norms and Quality management systems an important tool for Quality in Pharmaceutical Industry.

Validation concept is one of the important essential tools for Quality Management in Pharmaceutical Industry. It provides with Verification, Validation ,rather focuses on the question whether a system can perform its desired functions.

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Validation Concept has expanded through the years to encompass a wide range of activities from analytical methods used for the quality control of drug substances and drug products to computerized system for clinical trial, labelling or process control.[1]

It is a sequence of activities in order to demonstrate and document that a specific product can be reliably manufactured by the designed processes, usually, depending on the complexity of today's Pharmaceutical products, *the manufacturer should ensure that products will be consistently of a quality appropriate to their proposed use.* [2]

To achieve this with confidence, only in process control and finished product testing alone are not sufficient to assure product quality; but all factors including the services which could affect product quality must be correctly *designed, demonstrated to work effectively Consistently* and their performance is also regularly conformed so that consistent quality product is obtained. *For example, no sampling plan for carrying out sterility tests to a specified proportion of discrete units selected from a sterilization load is capable of demonstrating with complete assurance that all of the untested units are contaminated and not sterile .*

In recent years, many manufacturer's have attempted to define their view point and strategy for self inspecting their plants for *manufacturing, processing and packing, including hold study of drugs.* The manufacturers interpreted the GMP guidelines: evaluated by Food and drug Authority and the schedule M after due modification in 1988.[3]

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The word 'validation' simply means assessment of validity or action of proving effectiveness. According to European community for medicinal products, validation is action of proving in accordance with the principals of good manufacturing practices, that any procedure, process, equipment, material, activity or system actually leads to expected results.

Validation is a proof that a process works and this must be done using scientific and statistical principles. This is done to establish process capability and to confirm product acceptability.[4] Validation determines process variables and the acceptable limits for these variables and accordingly sets up appropriate in process controls, which specifies alert and action levels.[5]

Carrying out process validation is not only a Regulatory requirement, but also makes sure a sense from engineering as well as a business point of view, It is evident that pharmaceutical companies that are well versed in conducting process validation have a competitive advantage over those who are not[6].

Process validation is required, in both general and specific terms, by the Current Good Manufacturing Practices regulations for finished pharmaceuticals, 21 CFR parts 210 and 2117,8 . A requirement for process validation is set forth in general terms in sections 211.100 written procedures; deviations-which states, in parts; 'there shall be written procedures for production and process control designed to assure that the drug products have the identity , strength, quality, and purity they purport or are represented to posses'. Several sections of cGMP regulations state, validation requirement in more specific terms. Excerpts from some of the sections are:-section 211,100, sampling and testing of in -process materials and drug products.

Following are the areas where validation can be implied :

Analytical test methods, Instrument calibration, Process utility services, Raw materials, Packaging materials, Facilities, Manufacturing, Product design, Cleaning and Operators.

Pre-validation phase or the qualification phase ,which 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, storage and handling of in-process and finished dosage form, equipment qualification, installation qualification, master production documents, operational qualification, process capability.

A VMP is created when the project is complex, include high risk, and when more extensive and thoroughly verification and system review are required. If study is simple involving only one validation study /variables, a validation protocol may be used instead. The benefits of VMP includes, i) It provides the total pictures of the project. ii) It is a management tool for tracking progress. iii) Assignment of responsibility, which promote team work. iv) It identifies acceptance criteria before the start of validation.

Conclusion

The quality assurance of pharmaceutical product involves a number of factors. The complexity of modern day is that the drug products require more than the routine end product testing, as the end product testing is not sufficient to assure quality of finished product.

The review highlights various aspects on process elements, regulatory requirements, and validation documentation that are considered by regulatory agencies. The particular requirement of process validation will vary according to the nature of the pharmaceutical product and type of process. The broad concepts stated in this review have general applicability and provide an acceptable framework for building a comprehensive approach for the validation.

References

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