INTERNATIONAL RESEARCH JOURNAL OF PHARMACY
www.irjponline.com ISSN 2230 – 8407
Review Article

AN OVERVIEW: ROLE OF PROCESS VALIDATION IN TABLETS

Chawla Nirmaljot Singh[1]*, Rana A C[2], Saini Seema[1], Singh Gurpreet[1]
[1]Rayat Institute of Pharmacy, Department of Pharmaceutics, Railmajra, Distt. SBS Nagar, Punjab, India
[2]Rayat Institute of Pharmacy, Department of Pharmacology, Railmajra, Distt.SBS Nagar, Punjab, India

Article Received on: 15/11/11 Revised on: 21/12/11 Approved for publication: 18/01/12

*E-mail: nirmaljotchawla@gmail.com

ABSTRACT
The purpose of this work is to present an introduction and general overview on process validation of pharmaceutical manufacturing process especially tablet manufacturing process. Validation is the documented act of demonstrating that a procedure, process, and activity will consistently lead to the expected results. This type of validation is based on the physics of compression. It often includes the qualification of systems and equipment. It is a requirement for good manufacturing practices and other regulatory requirements. A properly designed system will provide a high degree of assurance that every step, process, and change has been properly evaluated before its implementation. Testing a sample of a final product is not considered sufficient evidence that every product within a batch meets the required specification. Three consecutive batches of tablets shall be taken up for process validation. Based on the result of these three batches the conclusion is drawn and Batch Manufacturing Record can be written once the validation process is complete.
KEYWORDS: Process Validation, Qualification, Good Manufacturing Practices, Consecutive, Batch Manufacturing Record

INTRODUCTION

Validation is a concept that has been evolving continuously since its first formal appearance in the United States in 1978. The concept of validation has expanded through the years to encompass a wide range of activities from analytical methods used for the quality control of the drug substances and drug products to computerized systems for clinical trials. Validation is therefore one element of quality assurance associated with a particular process, as the process differs so widely, there is no universal approach to validation and regulatory bodies such as FDA and EC who have developed general non-mandatory guide lines. Then word validation simply means, 'assessment of validity' or action of proving effectiveness'**.** A tablet formula is validated when the stochastic weight variations do not determine unacceptable variations of tablet properties.[1] According to European community for medicinal products, validation is 'action of proving', in accordance with the principles of GMP that any procedures, process, requirement, material, activity or system actually leads to expected results.

General Concept

The concept of validation was first proposed by two Food and Drug Administration (FDA) officials, Ted Byers and Bud Loftus, in the mid 1970's in order to improve the quality of pharmaceuticals (Agalloco 1995).[2] Assurance of product quality is derived from careful attention to number of factors including selection of quality parts and materials, adequate product and process design, control of the process, and in-process and end product testing. Due to the complexity of today's medical products, routine end product testing alone often is not sufficient to assure product quality for several reasons. Some end-products tests have limited sensitivity. E.g.:- In some cases, where end product testing does not several all variations that may occur in the product, which may have an impact on safety and effectiveness, destructive testing is required to show that the manufacturing process is adequate.

The basic goals of QA are as follows

Quality, safety, and effectiveness must be designed and built in to the product;
Quality cannot be inspected or tested in the finished product; hence each step of the manufacturing process must be controlled to maximize the probability that the finished product meets all quality and design specification. Quality control is the part of GMP, it is concerned with the sampling specification, testing and with organization documentation and release procedures.[3 4]

WHY VALIDATION?

- It would not be feasible to use the equipments without knowing whether it will produce the product we wanted or not.
- The pharmaceutical industry uses expensive materials, sophisticated facilities & equipments and highly qualified personnel.
- The efficient use of these resources is necessary for the continued success of the industry. The cost of product failures, rejects, reworks, recalls, complaints are the significant parts of the total production cost.
- Detailed study and control of the manufacturing process-validation is necessary if failure cost is to be reduced and productivity improved.[5]

The pharmaceutical industries are concerned about validation because of the following reasons

Assurance of quality

Without validation, a process that is well understood and in a state the confidence, control of quality of the product manufactured cannot be assured without validation

Cost reduction

Since each and every step in validation is monitored constantly there lesser rejects and reworks which would lead to an effective cost reduction.

Government regulation

Validation is considered to be an integral part of GMPs. Worldwide compliance with validation requirements is

necessary for obtaining approval to manufacture and to introduce new products.

The FDAs cGMP refer to the concepts of the validation in both sections. 211.110 & 211.113.

Section 211.110 states that, such control procedures shall be established to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in process materials and drug product.[6] The accuracy, sensitivity, specificity and reproducibility of test methods employed by the firm shall be established and documented.

HOW VALIDATION IS DONE?

The basic principle is characterized by harmony between the results obtained and requirements, which includes/supports.

- Specified requirements and objectives
- Available means
- Choices which are justified in relation to objectives
- Each stage should begin when the previous stage is over.

Certain dispositions have to be taken into account as to

- How restrictions should be defined?
- How norms should be dealt with
- How modifications should be dealt with?

Controlling the evolution will involve

- Setting data for decision making
- Evaluation before decision making
- Justifying the decision
- Follow-up

The following scheme may be suggested

- Aim versus objective
- Process as a whole and flow diagram
- Challenging the critical process variables
- Validation protocol
- Protocol versus report: procedures, sampling, testing, reporting and results.
- Evaluation and recommendations including frequency for re validation.

Responsible authorities for validation

The validation working party is convened to define, instigate, progress, collate, coordinate and ultimately, approve the entire effort, including all of the documentation generated. The working party would usually include the following staff members, preferably those with a good insight into the company's operation.

- Head of quality assurance
- Head of engineering
- Validation manager
- Production manager
- Specialist validation discipline (s)-all areas

TYPES OF VALIDATION

Analytical validation

Analytical validation is the evaluation of product quality attributes through testing, to demonstrate reliability is being maintained throughout the product life cycle and that the precision, accuracy, strength, purity and specification has not been compromised.

Equipment validation

Validation of equipments is known as qualification. Equipment validation is divided into installation Qualification (IQ), Operational Qualification (OQ), and Performance Qualification (PQ).

An IQ documents specific static attributes of a facility or item to prove that the installation of the unit has been correctly performed and that the installation specifications of the manufacturer have been met. After installation it must be ensured that the equipment can deliver operating ranges as specified in the purchase order. This is called OQ. The PQ's are concerned with proving that the process being investigated works as it is supposed to do.

Process validation

Process validation is "A documented program which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specification and quality attributes". Process validation should result in fewer product recalls and trouble shooting .process consistently under control requires less process support, will have less down time, fewer batch failures, and may operate more efficiently with greater output.[7] Process validation is divided into different types as follows

Prospective validation

It is defined as the establishment of documented evidence that a system does what it purports to do based on pre-planned protocol. This validation is usually carried out prior to the introduction of new drugs and their manufacturing process.

This approach to validation is normally undertaken whenever a new formula, process or facility must be validated before routine pharmaceutical formulation commences.

Retrospective validation

It is defined as the establishment of documented evidence that a system does what it purports to do based on review and analysis of historical data. This is achieved by the review of the historical manufacturing testing data to prove that the process has always remained in control.

Concurrent validation

It is similar to prospective, except the operating firm will sell the product during the qualification runs, to the public at its market price. This validation involves in process monitoring of critical processing steps and product testing.

Revalidation

It is the repetition of a validation process or a specific part of it.This is carried out when there is any change or replacement in formulation, equipment, plant or site location, batch size and in the case of sequential batches that do not meet product and process specifications. [8]

Computer system validation

Computer validation encompasses computers, which directly control process or system or collect analytical data. Computer validation includes the qualification of all software and hardware, which has an impact, direct or indirect, on the quality of a product. The validation approach to programmable logic controller (PLC) hardware and personal computers (PCs) is similar, both to one another and to the general overall approach top validation, in that the end user should define each requirement.[9]

PHASES OF VALIDATION

Design Qualification (DQ)

Document verification of the design of equipment and manufacturing facilities.

Installation Qualification (IQ)

Documented verification of equipment of system design and adherence to manufacturer's recommendations.

Operational qualification (OQ)
Documented verification of equipment or system performance in the target operating range.

Process performance qualification (PQ)
Documented verification that equipment or systems operate as expected under routine productions the operation is reproducible, reliable and in a state of control.

PHASES IN PROCESS VALIDATION
The activities relating to validation studies may be classified into three:

Phase1
This is the Pre-validation 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 and storage, and handling of in-process and finished dosage forms, equipment qualification, installation qualification master production document, operational qualification and process capacity.

Phase 2
This is the process validation phase. It is designed to verify that all established limits of the critical process parameter are valid and that satisfactory. Products can be produced even under the worst conditions.

Phase 3
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 crepitating procedures (SOPs), including change control procedures, have been followed. At this stage, the validation team comprising of individuals representing all major departments also assures that there have been no changes/deviations that should have resulted in requalification and revalidation. A careful design and validation of systems and process controls can establish a high degree of confidence that all lots or batches produced will meet their intended specifications. It is assumed that throughout manufacturing and control, operations are conducted in accordance with the principle of good manufacturing practice (GMP) both in general and in specific reference to sterile product manufacture. [10]

VALIDATION PROTOCOLS
Protocols should specify the following in detail

- General information
- Objective
- Background/revalidation
- Summary of development and technical transfer (form R& D or another site activity to justify in process testing and controls: any previous validations. Before formal cleaning validation programs were instituted, visual inspection was the primary means of determining equipment cleanliness.[11]
- List of equipments and their qualification status
- Facilities qualification
- Process flow chart
- Manufacturing procedure narrative
- List of critical processing parameters and critical excipients
- Sampling, test and specification
- Acceptance criteria

STRATEGY FOR VALIDATION OF METHODS
The validity of a specific method should be demonstrated in laboratory experiments using samples or standards that are similar to the unknown samples analyzed in the routine. The preparation and execution should follow a validation protocol preferably written in a step-by-step instruction format as follows.

- Develop a validation protocol or operating procedure for the validation
- Define the application purpose and scope of the method;
- Define the performance parameters and acceptance criteria
- Define validation experiments
- Verify relevant performance characteristics of the equipment
- Select quality materials, e.g. standards and reagents;
- Perform pre-validation experiments;
- Adjust method parameters and/or acceptance criteria, if necessary;
- Perform full internal (and external) validation experiments;
- Develop SOPs, for executing the method routinely; [12]
- Define criteria for revalidation
- Define type and frequency of system suitability tests and/or analytical quality control (AQC) checks for the routine; and
- Document validation experiments and results in the validation report.

CRITICAL FACTORS AND SAMPLE THIEF
Critical factors which affect conducting effective process validation

- The quality system (infrastructure) should support the validation effort by way of document control, calibration, preventive maintenance, etc.
- All the critical points of the process should be clearly identified
- The process should run using the extremes of the system at the critical points (worst case).
- Adequate run (data) are required to provide statistical support to demonstrate product consistency.
- 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.
- Before approving validation the area should be conformed for the requirement of validation.

SAMPLE THIEF
A significant improvement in sampling can be achieved with the use of sample thief, sometimes known as a grain thief of historical reasons. This device consists of 2 tubes one fitting tightly inside the other and with oolong holes cut through the tubes in corresponding positions. One end of the outer tube is fitted to a point to facilitate is insertion in to a bulk powder, the sampling procedure consists of rotating the inner tube to close the holes, inserting the device into the powder, rotating the inner tube to open the holes, allowing the powder to enter the device, rotating the inner tube once more to close the wholes and finally removing the thief from the bulk powder. The thief sampling is better method than merely scoping off the top of a bulk powder, it is still an inferior technique.

Even through most thieves have relatively sharp ends; the very act of plunging the thief through the bulk powder must perturb the sample to some degree. A compression force propagates ahead of the thief as it is pressed into the bulk, thus potentially changing the strata of the bulk and altering the wall of powder at the outer walls of the thief. Further more, because large particles will flow more easily than will small particles, an opened thief is liable to be filled preferentially with the coarse fraction of the particle distribution. [13]

Operation of sample Thief

a. The sleeve rotates so that the interior compartment is isolated form the bulk powder, while in the closed position, the thief is plunged into the central mass of the powder.
b. Once the thief is at the desired position, the unit is rotated so that the interior compartment is now exposed to the bulk powder. Powder flows into the thief compartment of its own accord.
c. Once the interior compartment of the thief is filled, the sleeve of the thief is rotated so that the interior compartment is again isolated from the bulk powder. The thief is then withdrawn form the powder, and the sample is analyzed. [14]

GENERAL NOTES

PROCESS VARIATIONS

The following are the sources, which may lead to variations in manufacturing operations. Variations are possible in

Materials (Raw material and packing components)

- Different suppliers of the same material
- Different batches form the same supplier

Equipment and facilities

- Different equipments for the same process
- Difference in adjustment of equipments
- Inadequate operating conditions
- Alternate equipments for the same process

Procedures

- Not clear and specific
- Inadequate
- Negligence by chance

Personnel

- Inadequate training and understanding
- Lack of interest
- Dishonesty, fatigue, carelessness
- Poor communication and co-operation

Instrument calibration

A pharmaceutical operation uses many measuring devices to control the process. An operator accomplishes either automatically by an appropriate feed back mechanism or through manual adjustment in this control. In either case proper validation of the measuring device is critical to the process. Some device that may require calibration are thermometer, pressure gauges, relative humidity meters, conductivity meters, timers, alarms etc. similarly some laboratory instruments that need calibration are balances, spectrophotometers, chromatography, computers, PH meters and rhymesters etc.[15] Thus calibration is carried out early in the validation program. The specification and frequency of calibration must be related to the use of the device or instrument in context of the overall process.

Critical support system

A support system is any general system that the plant needs to operate daily. These include air-handling system, electrical networks, vacuum for cleaning, water supply and others. For the purpose of validation we are concerned with the critical support system. These are the systems that must operate at a certain level in order to maintain the required level of quality of the final product. The qualifications of a critical plant support system consist of three phases viz. The first phase is designing a system or defining an existing system. The second is making sure that the installed system performs as designed if possible, challenging the system to make sure that normal and reasonable inputs, the system output acceptable.

Operator qualification

The operator is the most important element in a process. Thus the qualification of the operator by training and experience is absolutely essential to the success of the whole validation program. An untrained operator can neglect the work done in qualifying the other components of the process. The qualified operator is trained in all aspects of the job, technical, supervisory, productivity, GMP etc.

Raw material and packing material

Qualification of material involves the testing of specification for all critical parameters of the materials. These specifications must be set in the light for their purpose the end use of the product. Frequently the material will have specification in addition to those found in an official pharmacopoeia, such as particle size specification for an ingredient in table formulation. Importantly vendor must be qualified. Vendor qualification usually includes testing of samples and an audit of the vendor facility.

Equipment

The qualification of the equipment starts with the design or selection process, followed by installation and verification that the equipment functions are desired. Qualification of the equipment also requires the development of written procedures that describe the proper operation of the instrument/equipment, the development, preventive maintenance program, the validation of cleaning procedure, and the training of personnel using or supervising the use of equipment. Cleaning procedure must be adequate to remove product or dirt leaving acceptable (low) levels of cleaning agents, solvents etc. if the equipment must be sterile or progeny free the procedures to accomplish this have to be shown to be effective

Facilities

The qualification of the facility includes four phase-designs, construction, verification and on going maintenance and monitoring. At the design or planning phase, the purpose of the facility, the products to be manufactured, cGMP and efficiency requirements, as well as cost must be considered. The design of the critical system is most important. Flow of the material and personnel to avoid contamination has to be studied. Room surface especially in aseptic areas; have to be designed for effective sanitation. Finally everything needs to be documented. The constriction phase requires careful supervision to make sure that all design specification is being met. The process of verifying that the construction facility meets all established requirements stars when construction commences and ends with the installation and qualification of the equipment and critical systems.

Qualification of manufacturing stage

For each type of pharmaceutical dosage form there are various stages in manufacturing process that need to be qualified in order to validate the complete process.

Product design

The product design consists of the formulation, container/closure system, basic manufacturing procedure and quality control specification and methodology, chronologically; product design is the first elements of validation to be studied. Although product development is normally the responsibility of the R&D function, it is wise to involve plant personnel since their experience and knowledge of the plant capabilities can be very valuable. A poorly designed product can make it impossible to validate and control a process. It is important to emphasize the necessity of not making changes in a validated process without considering the consequences of the change, such as the need to be validating the process if the change is significant, the more frequently the problems and failures that occur are caused by changes made in a thoroughly studied and validated system.[16]

APPROACHES TO VALIDATION PROCESS

There are two basic approaches to the validation of the process itself (apart from the qualification of equipment used in production, the calibration of control and measurement instruments, the evaluation of environmental factors etc). These are the experimental approach, which is applicable to both prospective and concurrent validation, may involve.

- Extensive product testing
- Simulation process trials,
- Challenge/worst case trials, and control of process parameters.

One of the most practical forms of process validation, mainly for non-sterile products, is the final testing of the product to the extent greater than that required in routine quality control. It may involve extensive sampling far beyond that called for in routine quality control and specifications, and often for certain parameters only. Thus for instance, several hundred tablets per batch may be weighed to determine unit dose uniformity. The results are then treated statistically to verify the normality of the distribution and to determine the standard deviation from the average weight. Confidence limits for individual results and for batch homogeneity are also estimated. Strong assurance is provided that samples taken at random will meet regulatory requirements if the confidence limits are within compendia specifications.[17] In the approach based on analysis of historical data, no experiments are performed in retrospective validation, but instead all available historical data concerning a number of batches are combined and jointly analyzed, if production is proceeding smoothly during the period preceding validation and the data in process inspection and final testing of the product are combined and treated statistically. The restful including the outcome of process capability studies, trend analysis, etc., will indicate whether the process is under control or not.

THE VALIDATION REPORT

A written report should be available after completion of the validation. If found acceptable, it should be approved and authorized (signed and dated). [18] The report should include at least the following.

- Title and objective of study
- Reference to protocol
- Details of material
- Equipment
- Programs and cycles used
- Details of procedures and test methods.
- Result (compared with acceptance criteria), and
- Recommendations on the limit and criteria to be applied on future basis.[19 20]

CONCLUSION

Based on the obtained data and dissolution data from all three consecutive lots of first validation batch and finished product analytical data of all three validation batches, it can be concluded that process of manufacturing stands validated. So it is recommended to follow the same for forth coming batches

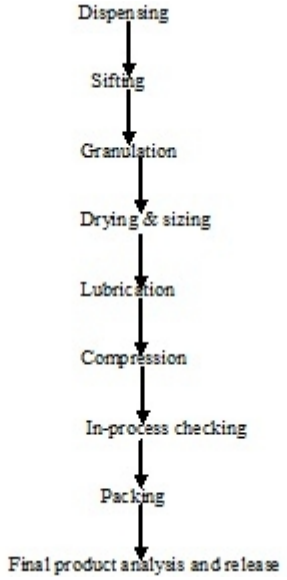
REFERENCES

1. Instituto Tecnica Farmaceutica, University of Parma, Via M. d'Azeglio 85, 43100, Parma, Italy; 1989. Vol. 15, No. 6-7 , p. 1047-1058
2. http://en.wikipedia.org/wiki/Validation_(drug_manufacture) ; Dated: 20th September,2011.
3. Ramamurthy S, Saravanakumar M. "Validation", The Eastern Pharmacist; 1997. p. 476.
4. Satish, M., Vadya, R., Paras, R., Fernandes, S.N. and Amonkar, N., **The Eastern Pharmacist.**, (1994), XXXVII, (443), p.51-53.
5. Sharma SK. "Validation of Pharmaceutical products and processes", The Eastern Pharmacist ;2001. p.263
6. Kieffer, R. G., PDA, **J. Pharm. Sci. Tech**., 1995, 49, (5), p.249.
7. Kiffer, R.G., **J.Pharm. Sci. Tech.,** (1995), 44, (5), p.249.
8. Good Manufacturing Practices for Pharmaceutical Products, In: Who Expert Committee on Specifications for Pharmaceutical Preparations, 32nd Report, Geneva, WHO, (1992), p.14-79.
9. Guidelines on General Principles of Process Validation, Food and Drug Administration, Maryland , 1984, p.4-25
10. Harder, S. W., In: Encyclopedia of Pharmaceutical Technology, Swarbrick, K. j., Boylan, J. C. (Eds.) Marcel Dekker: New York, 1995, vol. 2, p. 447-456.
11. Kaiser, H. J. and Minowitz, Analyzing Cleaning Validation Samples. www.Ivthome.com. Dated: 12th October, 2011
12. Klenzaids GMP Academy, **Express Pharma Pulse.**, (1998), Feb, p.12, 15.
13. Anurag SR, Joseph FN, Edward RA, Gail S, Peter W, and Rhona OL. "Process Validation-How Much to Do and When to Do It?" BioPharm; 2002. p.18-28.
14. J. Berman and J. A. Planchard, Marion Merrell Dow Inc., Formulation Development Department, 1995, Vol. 21, No. 11 ,p.1257-1283
15. "Process validation of solid dosage forms" – www.pfizerindia.com. Date 12th October,2011.
16. Rao MM., "Principles of validation", validation tools by corporate compliance, Mankind pharma, Paonta sahib; Sep 2004.p. 1-27.
17. The "In-house specification" of Ranbaxy laboratories ltd., Paonta sahib; p. 1-26.
18. "WHO guideline on GMP requirement", part 2-Validation. WHO Geneva; 1997.p.1-25.
19. FDA 483, Warning Letter, to Abraxis Bioscience ,Inc., 11777 San Vincente Blvd, Suite 550,Los Angeles, CA 90049; 18th Dec 2006.
20. FDA 483, Warning Letter, to Sanofi Pasteur, Inc., Discovery Drive, Swiftwater, Pennsylvania 18370; 20th June 2006.

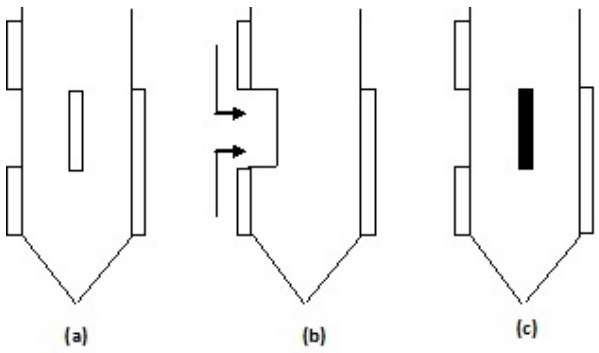
CONTROL PARAMETERS FOR CONSIDERATION IN SOLID DOSAGE FORMS DEVELOPMENT

UNIT OPERATION	PROCESS VARIABLE	METHOD RESPONSES
Dry mixing	Mixing time	Power consumption.
Granulation	Load, speed, binder Addition rate, Granulation time, Amperage Reading of impeller & chopper	Power consumption.
Drying	Load, inlet temperature, Air flow rate, drying time.	Moisture Content /LOD
Blending(mixing)	Load, speed, mixing time	Blend uniformity.
Compression	Press speed, feed rate, precompression force, Compression force.	Tablet weight, moisture content, hardness, thickness, dissolution, disintegration, Content uniformity.

PROTOCOL FOR PROCESS VALIDATION OF SOLID DOSAGE FORMS (TABLETS) PROCESS OVER VIEW



For sampling of homogenous liquid and thin emulsion generally use dipper bottle



Department /Designation	Responsibility
Manager-Production	Responsible for manufacturing of batches and review of protocol and report.
Manager – QC	Responsible for analysis of samples collected
Executive QC-	Responsible for samples collection and submission to QC
Manager-Maintenance	Providing utilities and engineering support
Executive – Production	Responsible for preparation of protocol and manufacturing of validation batches
Manager –QA	Responsible for protocol authorization and preparation of summary report.