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Review Article

AN OVERVIEW OF PHARMACEUTICAL VALIDATION: QUALITY ASSURANCE VIEW POINT

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ABSTRACT

Quality is the primordial intention to any industry and its products manufactured. Multiple views on obtaining such quality are the current interest in the pharmaceutical industry. Acquainted with a practice that puts us in common and routine convention ensured to deliver a quality that sounds globally in terms of a spoken quality is on the dais of pharmaceutical arena. Validation is the mean of catering enormous benefits to even more than the acceptable quality level which in the global standard scale. Lending importance to validation is increasingly profound in recent years. Validation is the art of designing and practicing the designed steps alongside with the documentation. Validation and quality assurance will go hand in hand, ensuring the through quality for the products. Hence, an emphasis made on to review that gives a detailed, overview of validation concept of designing, organizing and conducting validation trials. Additionally a view of validation against the quality assurance, drug development and manufacturing process has been discussed.

INTRODUCTION

The prime objective of any pharmaceutical plant is to manufacture products of requisite attribute and quality consistently, at the lowest possible cost. Although validation studies have been conducted in the pharmaceutical industry for a long time, there is an ever-increasing interest in validation owing to their industry's greater emphasis in recent years on quality assurance program and is fundamental to an efficient production operation. Validation is a concept that has evolved in united states in 1978.The concept of validation has expanded through the years to embrace a wide range of activities from analytical methods used for the quality control of drug substances and drug products to computerized systems for clinical trials, labelling or process control, Validation is founded on, but not prescribed by regulatory requirements and is best viewed as an important and integral part of cGMP. The word validation simply means assessment of validity or action of proving effectiveness. Validation is a team effort where it involves people from various disciplines of the plant.

Importance of Validation

1. Assurance of quality
2. Time bound
3. Process optimisation
4. Reduction of quality cost.
5. Nominal mix-ups, and bottle necks
6. Minimal batch failures, improved efficiently and productivity.
7. Reduction in rejections.
8. Increased output.
9. Avoidance of capital expenditures

10. Fewer complaints about process-related failures.
11. Reduced testing in process and in finished goods.
12. More rapid and reliable start-up of new equipments
13. Easier scale-up form development work.
14. Easier maintenance of equipment.
15. Improved employee awareness of processes.
16. More rapid automation.
17. Government regulation (Compliance with validation requirements is necessary for obtaining approval to manufacture and to introduce new products)

Planning for Validation

All validation activities should be planned. The key elements of a validation programme should be clearly defined and documented in a validation master plan (VMP) or equivalent documents.

- The VMP should be a summary document, which is brief, concise and clear.
- The VMP should contain data on at least the following:

1. Validation policy.
2. Organisational structure of validation activities.
3. Summary of facilities, systems, equipment and processes to be validated.
4. Documentation format: The format to be used for protocols and reports.
5. Planning and scheduling.
6. Change control.
7. Reference to existing document.
8. Incase of large projects, it may be necessary to create separate validation master plans.

Documentation

A written protocol should be established that specifies how qualification and validation will be conducted. The protocol should be reviewed and approved. The protocol should specify critical steps and acceptance criteria.

A report that cross-references the qualification and/or validation protocol should be prepared, summarizing the results obtained, commenting on any deviations observed, and drawing the necessary conclusions, including recommending changes necessary to correct deficiencies. Any changes to the plan as defined in the protocol should be documented with appropriate justification.

After completion of a satisfactory qualification, a format release for the next step in qualification and validation should be made as a written authorization.

Validation set up

To establish the desired attributes. These attributes include physical as well as chemical characteristics. In the case of parenterals, these desirable attributes should include stability, absence of pyrogens, and freedom from visible particles.

Acceptance specifications for the product should be established inorder to attain uniformity and consistently the desired product attributes, and the specifications should be derived from testing and challenge of the system on sound statistical basis during the initial development and production phases and continuing through subsequent routine production.

The process and equipment should be selected to achieve the product specification. For example; design engineers; production and quality assurance people may all be involved. The process should be defined with a great deal of specificity and each step of the process should be challenged to determine its adequacy. These aspects are important inorder to assure products of uniform quality, purity and performance.

TYPES/METHODS OF VALIDATION

Prospective validation

It is defined as the established documented evidence that a system does what it purports to do based on a pre-planned protocol. This validation usually carried out prior to distribution either of a new product or a product made under a revised manufacturing process. Performed on at least three successive production-size (Consecutive batches).

In Prospective Validation, the validation protocol is executed before the process is put into commercial use. During the product development phase, the production process should be categorized into individual steps. Each step should be evaluated on the basis of experience or theoretical considerations to determine the critical parameters that may affect the quality of the finished product. A series of experiment should be designed to determine the criticality of these factors. Each

experiment should be planned and documented fully in an authorised protocol. All equipment, production environment and the analytical testing methods to be used should have been fully validated. Master batch documents can be prepared only after the critical parameters of the process have been identified and machine settings, component specifications and environmental conditions have been determined.

Using this defined process a series of batches should be produced. In theory, the number of process runs carried out and observations made should be sufficient to allow the normal extent of variation and trends to be established to provide sufficient data for evaluation. It is generally considered acceptable that three consecutive batches/runs within the finally agreed parameters, giving product of the desired quality would constitute a proper validation of the process.

In practice, it may take some considerable time to accumulate these data. Some considerations should be exercised when selecting the process validation strategy. Amongst these should be the use of different lots of active raw materials and major excipients, batches produced on different shifts, the use of different equipment and facilities dedicated for commercial production, operating range of the critical processes, and a thorough analysis of the process data in case of Requalification and Revalidation.

During the processing of the validation batches, extensive sampling and testing should be performed on the product at various stages, and should be documented comprehensively. Detailed testing should also be done on the final product in its package.

Upon completion of the review, recommendations should be made on the extent of monitoring and the in-process controls necessary for routine production. These should be incorporated into the Batch manufacturing and packaging record or into appropriate standard operating procedures. Limits, frequencies and action to be taken in the event of the limits being exceeded should be specified.

Prospective validation should include, but not be limited to the following:

- Short description of the process.
- Summary of the critical processing steps to be investigated.
- List of the equipment/facilities to be used (including measuring, monitoring/recording equipment) together with its calibration status.
- Finished product specifications for release.
- List of analytical methods, as appropriate.
- Proposed in-process controls with acceptance criteria.
- Additional testing to be carried out, with acceptance criteria and analytical validation, as appropriate.
- Sampling plan.
- Methods for recording and evaluating results.
- Functions and responsibilities.
- Proposed timetable.

Using this defined process (including specified components) a series of batches of the final product may be produced under routine conditions. In theory, the number of process runs carried out and observations made, should be sufficient to allow the normal extent of variation and trends to be established and to provide sufficient data for evaluation. It is generally considered acceptable that three consecutive batches/runs within the finally agreed parameters would constitute a validation of the process.

Batches made for process validation should be the same size as the intended Industrial scale batches.

If it is intended that validation batches be sold or supplied, the conditions under which they are produced should comply fully with the requirements of Good Manufacturing Practice, including the satisfactory outcome of the validation exercise and the marketing authorization.

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, and also similar to retrospective validation.

This validation involves in-process monitoring of critical processing steps and product testing. This helps to generate and documented evidence to show that the production process is in a state of control.

- In exceptional circumstances it may be acceptable not to complete a validation programme before routine production starts.

- The decision to carry out concurrent validation must be justified, documented and approved by authorised personnel.
- Documentation requirements for concurrent validation are the same as specified for prospective validation.

Retrospective Validation

It is defined as the established documented evidence that a system does what it purports to do on the review and analysis of historical information. This is achieved by the review of the historical manufacturing testing data to prove that the process has always remained in control. This type of validation of a process for a product already in distribution.

Retrospective validation is only acceptable for well-established processes and will be inappropriate where there have been recent changes in the composition of the product, operating procedures or equipment.

Validation of such processes should be based on historical data. The steps involved require the preparation of a specific protocol and the reporting of the results of the data review, leading to a conclusion and a recommendation.

The source of data for this validation should include, but not be limited to batch processing and packaging records, process control charts, maintenance logbooks,

records of personnel changes, process capability studies, finished product data, including trend cards and storage stability results.

Batches selected for retrospective validation should be representative of all batches made during the review period, including any batches that failed to meet the specifications, and should be sufficient in number to demonstrate process consistency.

Additional testing of retained samples may be needed to obtain the necessary amount or type of data to retrospectively validate the process.

For retrospective validation, generally data from ten to thirty consecutive batches should be examined to access process consistency, but fewer batches may be examined if justified.

Some of the essential elements for Retrospective Validation are:

Batches manufactured for a defined period (minimum of 10 last consecutive batches).

Number of lots released per year.

- Batch size/strength/manufacturer/year/period.
- Master manufacturing/packaging documents.
- Current specifications for active materials/finished products.
- List of process deviations, corrective actions and changes to manufacturing documents.
- Data for stability testing for several batches.

CHANGE CONTROL

Written procedures should be in place to describe the actions to be taken if change is proposed to the starting material, product component, process equipment, process environment (or site), method of production or testing or any other change that may affect product quality or reproducibility of the process. Change control procedure should ensure that sufficient support data are generated to demonstrate that the revised process will result in a product of the desired quality, consistent with the approved specifications.

All changes that may affect product quality or reproducibility of the process should be formally requested, documented and accepted. The likely impact of the change of facilities, systems and equipment on the product should be evaluated,

including risk analysis. The need for, and the extent of, requalification and revalidation should be determined.

REVALIDATION

Re-validation provides the evidence that changes in a process and/or the process environment that are introduced do not adversely affect process characteristics and product quality. Documentation requirements will be the same as for the initial validation of the process.

Facilities, systems, equipment and processes, including cleaning, should be periodically evaluated to confirm that they remain valid. Where no significant changes have been made to the validated status, a review with evidence that facilities, systems, equipment and processes meet the prescribed requirements fulfils the need for revalidation.

Revalidation becomes necessary in certain situations. Some of the changes that require validation are as follows:

- Changes in raw materials (physical properties such as density, viscosity, particle size distribution and moisture etc., that may affect the process or product).
- Changes in the source of active raw material manufacturer.
- Changes in packaging material (primary container / closure system)
- Changes in the process (e.g., mixing time, drying temperatures and batch size)
- Changes in the equipment (e.g., addition of automatic detection system). Changes of equipment which involve the replacement of equipment on a "like for like" basis would not normally require re-validation except that this new equipment must be qualified.
- Changes in the plant / facility.
- A decision not to perform re-validation studies must be fully justified and documented.

BASIC CONCEPT OF PROCESS VALIDATION

- Calibration, verification and maintenance of process equipment.
- Prequalification or revalidation.
- Establishing specifications and performance characteristics.
- Selection of methods, process and equipment to ensure the product meets specifications.
- Qualification or validation of process and equipment.
- Testing the final product, using validated analytical methods, in order to meet specifications.
- Challenging, auditing, monitoring or sampling the recognised critical key steps of the process.

Phases in process validation

The activities relating to validation studies may be classified into three phases:

Phase 1

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 forms, Equipment qualification, Installation qualification, master production documents, Operational qualification, Process capability.

Phase 2

Process validation phase (Process Qualification phase) 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 case" conditions.

Phase 3

Validation Maintenance phase requiring frequent review of all process related documents, including validation audit reports to assure that there have been no changes, deviations, failures, modifications to the production process, and that all SOPs have been followed, including change control procedures.

At this stage the Validation Team also assures that there have been no changes / deviations that should have resulted in requalification and revalidation.

ORGANISATION FOR VALIDATION

Validation organisation can be divided into three basic areas;

1. Establishing the organisation.
2. Operating it from a quality and cost effectiveness basis.
3. Maintaining a functioning organisation.

Establishing the organisation

Formulating a department mission is necessary so that, not only process validation staff members understand the breadth of their job, but also the other corporate groups with whom there is interaction, can also understand.1

In some organisation senior staff members representing the process validation, R&D, Quality Assurance, Production and Engineering functions combine to form advisory or steering committees for the validation programme. This committee can prove extremely valuable to the validation program by defining the mission, as well as by making decisions on specific issues of concern; validation professionals provide sufficient technical information to this committee.

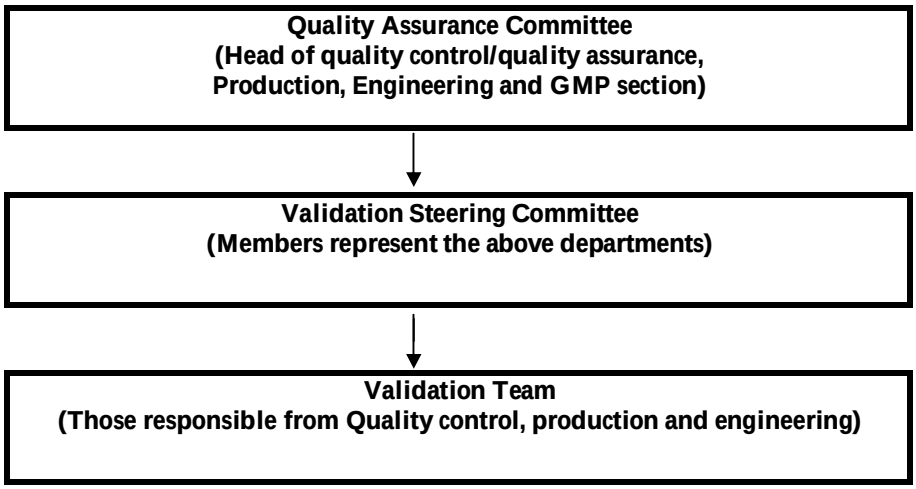

Fig. 1

Departments responsible

- Site validation committee: - Develop site master validation plan.
- Manufacturing department: - Prepares the batches as though their routine production batches.
- Quality assurance: - Ensure compliance and that documentation, procedures are in place. Approves protocols and reports.
- Quality controls: - Perform testing contracts validation testing and reviews protocol and report as needed.
- Research and development: - Deals with product design.
- Engineering department: - Installation, quality and certify plant, facilities, equipment and support systems.

Validation team

A multidisciplinary team is primarily responsible for conducting and supervising validation studies. Personnel qualified by training and experience in a relevant discipline may conduct such studies.

Responsibilities of validation team

- Creates updates and reviews/approves individual project validation plans and validation deliverables.
- Ensures validation compliance with the company validation master plan and project validation plan. As mentioned in fig No:2
- Coordinates, implements, verify elements of VMP.
- Consults on, evaluates and approves changes.
- Reviews and approves IQ/OQ/PQ procedures and plans.
- Reviews test results and makes recommendations regarding release.
- Assess risks and develops contingency plan.

Elements of validation

The validation of a process requires the qualification of each of the important elements of the process. The relative importance of an element may vary from process to process. Some of the elements commonly considered in a process validation study are presented below.

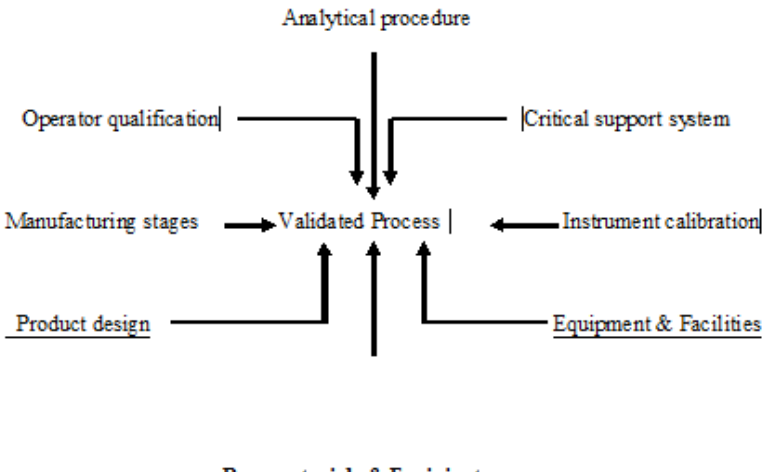

Fig. 2

QUALIFICATION

Design qualification

- The first element of validation of new facilities, systems or equipment could be design qualification (DQ)
- The compliance of the design with GMP should be demonstrated and documented.

Installation qualification

I.Q is a method of establishing with confidence that all major processing, packaging equipment and ancillary systems are in conformance with installation specifications, equipment manuals, schematics and engineering drawings. This stage of validation includes examination of equipment design, determination of calibration, maintenance and adjustment requirements.

Installation qualification (IQ) should be performed on new or modified facilities, systems and equipment.

IQ should include, but not be limited to the following:

Installation of equipment, piping, services and instrumentation checked to current engineering drawings and specifications.

- Collection and collation of supplier operating and working instructions and maintenance requirements.
- Calibration requirements.
- Verification of materials of construction.
- Description of equipment.
- Piping & Instrument diagrams.
- Principle of operation.
- Facility functional specifications.
- Design requirements.
- Equipment utility requirements, equipment specification, equipment features.

Operational qualification

The conduct of an Operational qualification (OQ) should follow an authorised protocol. The critical operating parameters for the equipment and systems should be identified at the O.Q stage. The plans for the O.Q should identify the studies to be undertaken on the critical variables, the sequence of those studies and the measuring equipment to be used and the acceptance criteria to be met.

Studies on the critical variables should include a condition or a set of conditions encompassing upper and lower processing and operating limits referred to as "worst-case" conditions. The completion of a successful OQ should allow the finalization of operating procedures and operator instructions documentation for the equipment. This information should be used as the basis for training of operators in the requirements for satisfactory operation of the equipment.

The completion of satisfactory I.Q and O.Q exercises should permit a formal "release" of the equipment for the next stage in the process validation exercise as long as calibration, cleaning, preventive maintenance and operator training requirements have been finalized and documented.
Operation qualification (OQ) should follow Installation qualification.

OQ should include, but not be limited to the following:

- Tests that have been developed from knowledge of processes, systems and equipment.
- Tests to include a condition or a set of conditions encompassing upper and lower operating limits, sometimes referred to as "worst case" conditions.
- The completion of a successful Operational qualification should allow the finalization of calibration, operating and cleaning procedures, operator training and preventive maintenance requirements. It should permit a formal "release" of the facilities, systems and equipment.
- Equipment operational procedures established and challenged.
- Equipment control functions.
- Calibration requirements & schedules established.
- Maintenance requirements & established schedules.

Performance qualification

Performance qualification (PQ) should follow successful completion of Installation qualification and Operational qualification.

- PQ should include, but not be limited to the following:
- Tests, using production materials, qualified substitutes or simulated product, that have been developed from knowledge of the process and the facilities, systems or equipment.
- Tests to include a condition or set of conditions encompassing upper and lower operating limits.

Although PQ is described as a separate activity, it may in some cases be appropriate to perform it in conjunction with OQ.
Qualification of established (in-use) facilities, systems and equipment

Evidence should be available to support and verify the operating parameters and limits for the critical variables of the operating equipment. Additionally, the calibration, cleaning, preventive maintenance, operating procedures and operator training procedures and records should be documented.

Regulations of Validation

The three basic and most important reasons for validation are quality assurance, economics and compliance.

1. **Quality assurance**

Product quality cannot be assumed for a process by routine quality control testing because of the limitation of statistical sampling and the limited sensitivity if the finished product testing. Quality variations among units within a batch, or among different batches, are seldom detected by testing of finished product samples. Validation challenges the adequacy and reliability of a system or process to meet pre-determined criteria. A successful validation, therefore, provides a high degree of confidence that the same level of quality is consistently built into each unit of the finished product, from batch to batch. The Pharmaceutical Manufacturers Association (PMA) and the FDA have recognized the product quality assurance concept of validation.

2. **Economics**

The direct economics benefit of validation is a reduction in the cost associated with process monitoring, sampling and testing. The consistency and reliability of a validated process to produce a quality product provide indirect cost savings resulting from a decrease or elimination of product rejections, reworks and retesting. Final release of the product batch would be expedited and free of delays and complications caused by lengthy investigations of process or analytical variances. In addition, product quality complaints and potential product recalls would be minimized.

3. **Compliance**

Specific current Good Manufacturing Practices (cGMP) references to variation are found in following sections of 21CFR211
211.884(d) – Variation of suppliers test result for components when these

results are accepted in lieu of in-house testing after receipt.

211.110(a) – Validation of manufacturing process to ensure batch uniformity and integrity of drug products.

211.165(e) – Validation of analytical methodologies.

The requirement of validation is also implied in 211.100(a). This section of GMP requires that written procedures and process controls be established to ensure that the drug products have to "identify strength, quality and purity are represented to possess".

The FDA's draft Mid Atlantic Pharmaceutical Inspection Guidance Program for Prescription Drug Plants, issued in January 1990,emphasis the importance of validation in the manufacturing process.

Process validation and quality assurance

The relationship of quality assurance and process validation goes well beyond the responsibility of any quality assurance (QA) function. Nevertheless, it is a fair to say that process validation is a QA tool, because it establishes a quality standard for the specific process.

Quality assurance in pharmaceutical companies embodies the effort to assure that products have the strength, purity, safety and efficacy represented in the company's new drug application (NDA) filings.

Although quality assurance is usually designated as a departmental function, it must also be an integral part of an organization's activities. When process validation becomes a general objective of the technical and operational groups within an organization, it becomes the driving force for quality standards in development work, engineering activities, quality assurance, and production.

The quality assurance associated with the pharmaceutical development effort includes the following general functions:

1. To ensure that a valid formulation is designated.
2. To qualify the process that will be scaled up to production-size batches.
3. To assist the design of the validation protocol.
4. To manufacture the bio batches for the clinical program, which will become the object of the FDA's preapproval clearance.

To work with production and engineering to develop and carry out the qualification program for production equipment and facilities / process systems.

- To develop validated analytical methods to allow:
- The stability program to be carried out.
- The testing of raw materials and finished product
- The development of release specifications for the raw materials and finished product.
- The testing of processed material at certain specified stages.

Quality assurance is the effort taken to ensure compliance with government regulations for the systems, facilities, and personnel involved with manufacturing products. QA audits will be quite varied in scope to achieve this assurance. These responsibilities include batch record reviews, critiques of product design, process validation activity, and, possibly, audits of other departments' operations.

A typical Validation Blueprint of Equipment validation

Introduction

1. Installation qualification
- Facilities
- Utilities
- Equipment
2. Operation qualification
- Testing Protocols for Utilities and Equipment
3. Validation
- Testing protocols for products and Cleaning systems
4. Documentation
5. Validation of the QA testing laboratory
6. SOPs
7. Training of personnel
8. Organization charts
9. Schedule of events

When an organization follows the precepts of total quality management (TQM), the concept of continuous improvement would routinely be used.

When process validation is used as a quality assurance tool instead of a final examination, an organization's operations will improve or stay at the highest quality level possible. The effort will be properly documented, and the overall attitudes of all the affected personnel will be positive. Finally, a more logical

approach to pre approval inspections and other FDA technical interactions will be affected.

When the validation activity becomes the focal point of an organizational unit's effort to carry out its own technical responsibilities, quality standards will be maintained for the product and manufacturing process from the design and development stages and throughout the commercial life of the product.

The concept of validation had to be redefined and re-evaluated to accommodate the technical changes. Traditional validation concepts and procedures that were acceptable years ago may no longer be applicable to today's operations and equipment.

A practical understanding of the validation concepts and when and how to apply them is of greater importance to ensure a meaningful, efficient, effective, and economical validation program. Because practicality and compliance are both important aspects of validation. Finally, as with any project, the validation is not complete without the necessary documentation. Special attention should be afforded to the physical appearance of the report, as well as its technical contents.

Note for guidance on process validation

Validation is the act of demonstrating and documenting that a process operates effectively.

Process validation is the means of ensuring and providing documentary evidence that processes (within their specified design parameters) are capable of consistently producing a finished product of the required quality.

In terms of pharmaceutical process validation it is intended that, all the critical elements in a manufacturing process for a pharmaceutical product, from development of the process through a final validation at the production scale should be covered.

It is recognised that the term validation is intended to apply to the final verification at the production scale, (typically 3 production batches)

It is essential that only valid manufacturing processes are used, it is increasingly that data should be submitted in the application for marketing authorisation demonstrating the validity of the given process.

Thus the progress from pre-formulation formulation pilot manufactures industrial scale manufacture should be shown in the marketing authorisation application dossier to be logical, reasoned and continuous.

Scope

This note for guidance is intended to give the applicant for marketing authorisation in relation to studies to evaluate the manufacturing process and/or data which need to be generated to studies to validate the processes used for the finished product.

Relationship Between Development Studies and Process Validation Data

It is expected that during development stage, the manufacturer of the product should gain sufficient information about the behaviour and physical and chemical properties of the drug substance, the composition of the product in term of active ingredient(s) and key excipients and the manufacturing processes to clearly define the critical steps in the manufacturing process. Critical parameters of the product should be identified at an early stage; for example the dissolution rate of an active substance and the effect of the presence, type and amount of lubricant.

Information generated during the development stage should thus be used to identify and evaluate the critical pharmaceutical process parameters, which may need to be examined and possibly controlled in order to ensure batch-to-batch reproducibility.

Inorder to define these critical parameters it may be necessary to challenge the process by making deliberate changes to demonstrate robustness of the process and define the limits of tolerance.

Relationship between Method of manufactures and Process Validation Data

Having defined and justified a particular method of manufacture based on a consideration of the physical and chemical properties of the active ingredient, the key excipients, the choice of formulation and impact of processing on the product quality and stability, the manufacturer should progress to fully describe the manufacturing process.

Such a description should address also the need and value of in-process controls and the manufacturer's approach to process optimisation. The evaluation of

the process should provide adequate proof of the feasibility of the process at the production scale thereby ensuring the consistent quality of the product in line with the approved specification.

Relationship between Process Validation and Specification of the Finished Product

The ICH guideline Q6A specification for new drug substances and products permits skip lot testing, i.e., replacement of routine verification of certain tests on a batch by batch basis.

In addition, data generated through process evaluation or validation can be used to justify why certain test need not be conducted routinely on the finished product at release.

Data submission

Validation data should be generated for all products to demonstrate the adequacy of the manufacturing process. It is recognized that, at the time of submission, process validation data may not always be available. Nevertheless it is essential that valid manufacturing processes are always utilized. Validation data should be held at manufacturing location and made available for verification by concerned authorities.

Laboratory scale batches

These are produced at the research and early development laboratory stage: they may be of very small size (e.g. one tenth of intended production batch). These batches may find many uses, for example to support formulation and packaging development, clinical and / or pre-clinical studies.

The data derived from these batches assist in the evaluation and definition of critical product performance characteristics and thereby enables the choice of appropriate manufacturing process.

Pilot Batches

These may be used in the process development or optimisation stage may be used to support formal stability studies and also support pre-clinical and clinical evaluation. Pilot Batch size should correspond to at least 10% of the production scale batch, i.e.such that the multiplication factor for the scale-up does not exceed 10.For oral dosage forms this size should generally be 10% of the production scale or 100,000 units whichever is the greater.

The role of pilot scale batches is to provide data predictive of the production scale product. It may be necessary to further develop and optimise the manufacturing process using pilot scale batches. The pilot scale batch therefore provides the link between process development and industrial production of the product.

The purpose of the pilot batch is to challenge the method proposed for routine production, i.e. to analyse and evaluate:

- The difficulties and the critical points of the manufacturing process.
- The apparatus and methods most appropriate to large scale production.
- To summarize, the production of pilot batches should provide a high level of assurance that the product and process will be feasible on an industrial scale.

Production Scale Batches

These batches are of the size, which will be produced during the routine marketing of the product. Data on the production scale may not always available prior to granting marketing authorization.

Where production scale data are not available or presented at the time of submission, the two-stage approach outlined below should be followed.

First a thorough evaluation and characterization of the critical process parameters at laboratory or pilot scale, followed by a formal validation programme on production scale batches for which the "validation scheme" has been described.

Data requirements

Since it is not generally considered useful to conduct full validation studies on the pilot scale batches, the validation scheme outlined should be completed for each product for subsequent verification at the production scale.

CONCLUSION

Validation has been proven assurance for the process efficiency and sturdiness and it is the full fledged quality attributing tool for the pharmaceutical industries. Validation is the commonest word in the areas of drug development, manufacturing and specification of finished products. It also renders reduction in the cost linked with process monitoring, sampling and testing. Apart from all the

consistency and reliability of a validated process to produce a quality product is the very important for an industry.

REFERENCES

1. Carleton FJ and Agalloco JP. Validation of pharmaceutical processes, sterile products., second edition., 1 to 16.
2. Britain H.G pharmaceutical technology., July 2002; 68 to 70.
3. Nash RA and Berry IR. Pharmaceutical Process Validation., second edition, Marcel Dekker inc., 167-188,200-202,205.
4. European Commission Enterprise Directorate General Single market, regulatory environment, industries under vertical legislation Pharmaceuticals and Cosmetics Brussels, July 2001. EU Guide to Good Manufacturing Practice, Qualification and validation.
5. FDA guidelines on General Principles of Process Validation (May 1987)
6. Chapman KG, Amer G, Brower G, GreenC, Hall WE and Harpaz D. Journal of Validation Technology. 2000;6:505-506.
7. Health Products and Food Branch Inspectorate, Guidance Document Validation, Guidelines for Pharmaceutical Dosage Forms.
8. Validation Master Plan, www.labcompliance.com.
9. The European agency for evaluation of medical products, London Note for Guidance on Process Validation, 2001.
10. British Pharmacopoeia 2002, Department of Health, Scottish Home and Health department, Volume I,736.
11. Howard T. Fuller Six Sigma for Validation, Journal of Validation Technology. 2000; 6(4):749-765,751.