REVIEW ARTICLE

VALIDATION: A CRITICAL PARAMETER FOR QUALITY CONTROL OF PHARMACEUTICALS

Tangri Pranshu*, Rawat Prakash Singh, Jakhmola Vikash, Lakshmayya

Grd(pg)imt, department of pharmacy, Dehradun, uttarakhand-248001, INDIA

Corresponding Author's Email: prianshu_tangri@yahoo.co.in, Phone: 09927760066

Received 11 March 2012; Revised 16 April 2012; Accepted 01 May 2012, Available online 15 May 2012

ABSTRACT

The current objective of this review is to understand the types of validation, its basic concept and applicability in the pharmaceutical industry. Method validation is the process by which it is established that performance characteristics of the method meet the requirements for the intended analytical applications. Methods need to be validated or revalidated before their introduction into routine use. The most compelling reasons to optimize and validate pharmaceutical productions and supporting processes are quality assurance and cost reduction .the basic principles of quality assurance has as their goal and the production of articles that are fit for there intended use. These principles are Quality, safety, and effectiveness must be designed and built in to the product, quality cannot be inspected or tested in the finished products and each step of the manufacturing process must be controlled to maximize the probability that the finished product meets all quality and design specification. Through this review the authors make an effort to explain the concept of validation and provide an insight to its importance in the pharmaceutical industry.

Key words: validation, process, analytical, qualification, quality control.

INTRODUCTION

Method validation is the process by which it is established that performance characteristics of the method meet the requirements for the intended analytical applications. Methods need to be validated or revalidated before their introduction into routine use.[1] The International Conference on Harmonization (ICH) of Technical Requirements for the Registration of Pharmaceuticals for Human Use[2] has developed a text on the validation of analytical procedures. The United States Food and Drug Administration (USFDA) have proposed guidelines on submitting samples and analytical data for methods validation[5-7]. The United States Pharmacopoeia (USP) has published specific guidelines for method validation for compound evaluation[8]. The document includes definitions for eight validation characteristics. An extension with more detailed

Methodology is in preparation and nearly completed[3]. The United States Environmental Protection Agency (US EPA) prepared a guidance for methods development and validation for the Resource Conservation and Recovery Act (RCRA)[4]. The pharmaceutical industry uses methodology published in the literature [9,10]. The most comprehensive document was published as the 'Conference Report of the Washington Conference on Analytical Methods Validation: Bioavailability, Bioequivalence and Pharmacokinetic Studies held in 1990 (sponsored by the American Association of Pharmaceutical Scientists, the AOAC and the US FDA, among others)[10]. The report presents guiding principles for validation of studies in both human and animal subjects that may be referred to in developing future formal guidelines. Representatives of the pharmaceutical and chemical industry have published papers on the validation of analytical methods. Hokanson [11,12] applied the life cycle approach, developed for computerized systems, to the validation and revalidation of methods. Green[13] gave a practical guide for analytical method validation with a description of a set of minimum requirements for a method. Renger and his colleagues [14] described the validation of a specific analytical procedure for the analysis of theophylline in a tablet using high performance thin layer chromatography (HPTLC). The validation procedure in that article is based on requirements for European Union multistate registration. Wegscheider [15] has published procedures for method validation with special focus on calibration, recovery experiments, method comparison and investigation of ruggedness. The Association of Official Analytical Chemists (AOAC) [16] has developed a Peer-Verified Methods validation program with detailed guidelines on what parameters should be validated. This article gives a review and a strategy for the validation of analytical methods for both in-house developed as well as standard methods and a recommendation on the documentation that should be produced during and at the end of method validation.

Definition:

•Documented evidence that the manufacturing process consistently produces product that meets predetermined specifications.

•Manufacturing process validation consists of successfully manufacturing at least threefull-scale batches in succession, which pass all in-process and product quality attributes.

VALIDATION PROCESS

The validation process consists of identifying and testing all aspects of a process that could affect the final test or

product. Prior to the testing of a process, the system must be properly qualified. Qualification includes the following steps: (These steps are common practice for equipment IQ, OQ and PQ).[17]

- Design qualification (DQ)- Defines the functional and operational specification of the instrument, program, or equipment and details the rationale for choosing the supplier.
- Installation qualification (IQ) – Demonstrates that the process or equipment meets all specifications, is installed correctly, and all required components and documentation needed for continued operation are installed and in place.
- Operational qualification (OQ) – Demonstrates that all facets of the process or equipment are operating correctly.
- Performance qualification (PQ) – Demonstrates that the process or equipment performs as intended in a consistent manner over time.
- Component qualification (CQ) – is a relatively new term developed in 2005. This term refers to the manufacturing of auxiliary components to ensure that they are manufactured to the correct design criteria. This could include packaging components such as folding cartons, shipping cases, labels or even phase change material. All of these components must have some type of random inspection to ensure that the third party manufacturer's process is consistently producing components that are used in the world of GMP at drug or biologic manufacturer.

TYPES OF VALIDATION

- Equipment validation
- Process validation
- Analytical method validation
- Cleaning validation

EQUIPMENT VALIDATION

Installation Qualification(IQ)

Operational Qualification(OQ)

Performance Qualification(PQ)

Installation Qualification (IQ)

This is the first step in validation. This protocol insures that the system/equipment and its components areinstalled correctly and to the original manufacturer's specifications. Calibration of major equipment, accessory equipment, and/or utilities shouldbe performed in this step as well

IQ provides documented evidence that the equipment or system has been developed, supplied and installed in accordance with design drawings, the supplier's recommendations and In-house requirements. Furthermore, IQ ensures that a record of the principal features of the equipment or system, as installed, is available and that it is supported by sufficient adequate documentation to enable satisfactory operation, maintenance and change control to be implemented.[18]

Operational Qualification (OQ)

This step proceeds after the IQ has been performed. In the OQ, tests are performed on the critical parameters of thesystem/process. These are usually the independent and/or manipulated variables associated with the system/equipment.[5-7] All tests data and measurements must be documented in order to set a baseline for the system/equipment. OQ provides documented evidence that the equipment operates as intended throughout the specified design, operational or approved acceptance range of the equipment, as applicable. In cases where process steps are tested, a suitable placebo batch will be used to demonstrate equipment functionality. All new equipment should be fully commissioned prior to commencing OQ to ensure that as a minimum the equipment is safe to operate, all mechanical assembly and pre-qualification checks have been completed, that the equipment is fully functional and that documentation is complete.[13-15]

Performance Qualification (PQ):

This is the third and final phase of validation. This phase tests the ability of the process to perform over long periods of time within tolerance deemed acceptable. PQ is performed on the manufacturing process as a whole. Individual components of the system are not tested individually. The purpose of PQ is to provide documented evidence that the equipment can consistently achieve and maintain its performance specifications over a prolonged operating period at a defined operating point to produce a product of pre-determined quality. The performance specification will reference process parameters, in-process and product specifications.[20-22] PQ requires three product batches to meet all acceptance criteria for in-process and product testing. For utility systems, PQ requires the utility medium to meet all specifications over a prolonged sampling period.[3-5]

PROCESS VALIDATION

"Process validation" is establishing documented evidence whichprovides a high degree of assurance that a specific process consistentlyproduce a product meeting it's predetermined specifications and quality attributes"[5,6]

Types of Process Validation

- Prospective validation
- Retrospective validation
- Concurrent validation
- Revalidation

Prospective validation:

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.[20,21] 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 broken down 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 experiments should be designed to determine the criticality of these factors. Each experiment should be planned and documented fully in an authorized 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. 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. It is a confirmation on the commercial three batches before marketing. 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 actions to be taken in the event of the limits being exceeded should be specified. It may be possible and acceptable in particular circumstances for a manufacturer that uses the same process for several related products to develop a scientifically sound validation plan for that process rather than different plans for each product manufactured by that process.[13,14]

Retrospective validation:

The retrospective validation option is chosen for established products whose manufacturing processes are considered stable and when on the basis of economic considerations alone and resource limitations, prospective validation programs cannot be justified. Prior to undertaking retrospective validation, wherein the numerical in-process and/or end-product test data of historic production batches are subjected to statistical analysis, the equipment, facilities and subsystems used in connection with the manufacturing process must be qualified in conformance with CGMP requirements.[14-17] The basis for retrospective validation is stated in 21CFR 211.110(b): "Valid in-process specifications for such characteristics shall be consistent with drug product final specifications and shall be derived from previous acceptable process average and process variability estimates where possible and determined by the application of suitable statistical procedures where appropriate." Using either data-based computer systems or manual methods, retrospective validation may be conducted in the following manner:[18]

1. Gather the numerical data from the completed batch record and include assay values, end-product test results, and in-process data.

2. Organize these data in a chronological sequence according to batch manufacturing data, using a spreadsheet format.

3. Include data from at least the last 20–30 manufactured batches for analysis. If the number of batches is less than 20, then include all manufactured batches and commit to obtain the required number for analysis.

4. Trim the data by eliminating test results from noncritical processing steps and delete all gratuitous numerical information.

5. Subject the resultant data to statistical analysis and evaluation.

6. Draw conclusions as to the state of control of the manufacturing process based on the analysis of retrospective validation data.

7. Issue a report of your findings (documented evidence).

Concurrent validation:

In-process monitoring of critical processing steps and end-product testing of current production can provide documented evidence to show that the manufacturing process is in a state of control. Is similar to prospective, except the operating firm will sell the product during the qualification runs, to the public at its market price.[19] This validation involves in process monitoring of critical processing steps and product testing. Retrospective validation is only acceptable for well established detailed processes that include operational limits for each critical step of the process and will be inappropriate where there have been recent changes in the formulation of the product, operating procedures, equipment and facility. The source of data for retrospective validation should include amongst others, batch documents, process control charts, maintenance log books, process capability studies, finished product test results, including trend analyses, and stability results. For the purpose of retrospective validation studies, it is considered acceptable that data from a minimum of ten consecutive batches produced be utilized. When less than ten batches are available, it is considered that the data are not sufficient to demonstrate retrospectively that the process is fully under control. In such cases the study should be supplemented with data generated with concurrent or prospective validation.[7-9]

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.

• Trend analyses including those for quality related complaints.

Revalidation:

Almost all GMP texts recommend that whenever there are significant changes in the facility, equipment or process, revalidation should be carried out. The FDA process validation guidelines refer to a quality assurance system in place that requires revalidation whenever there are changes

 ISSN: 2250-1177 CODEN: JDDTAO

in packaging (assumed to be the primary container-closure system), formulation, equipment or processes (meaning not clear) which could impact on product effectiveness or product characteristics and whenever there are changes in product characteristics.
Conditions requiring revalidation study and documentation are listed as follows:[11]

- Change in a critical component (usually refers to raw materials).
- Change or replacement in a critical piece of modular (capital) equipment.
- Change in a facility and/or plant (usually location or site).
- Significant (usually order of magnitude) increase or decrease in batch size Sequential batches that fail to meet product and process specifications.

Benefits of process validation

• Increased throughput

• Reduction in rejections and reworks

• Reduction in utility costs

• Avoidance of capital expenditures

• Fewer complaints about process related failures

• Reduced testing in process and finished goods

• More rapid and accurate investigations into process deviations

• More rapid and reliable start-up of new equipment

• Easier scale-up from development work

• Easier maintenance of the equipment

• Improved employee awareness of processes

• More rapid automation

ANALYTICAL METHOD VALIDATION:

There are many reasons for the need to validate analytical procedures. Among them are regulatory requirements, good science, and quality control requirements. The *Code of Federal Regulations* (CFR) 311.165c explicitly states that "the accuracy, sensitivity, specificity, and reproducibility of test methods employed by the firm shall be established and documented."Of course, as scientists, we would want to apply good science to demonstrate that the analytical method used had demonstrated accuracy, sensitivity, specifi city, and reproducibility. Finally management of the quality control unit would definitely want to ensure that the analytical methods that the department uses to release its products are properly validated for its intended use so the product will be safe for human use.[1-3]

Analytical methods need to be validated, verified, or revalidated in the following instances:

- Before initial use in routine testing
- When transferred to another laboratory
- Whenever the conditions or method parameters for which the method has been validated change (for example, an instrument with different characteristics or samples with a different matrix) and the change is outside the original scope of the method.[7]

Cycle of analytical methods

The analytical method validation activity is not a one - time study. An analytical method will be developed and validated for use to analyze samples during the early development of an active pharmaceutical ingredient (API) or drug product. As drug development progresses from phase 1 to commercialization, the analytical method will follow a similar progression. The final method will be validated for its intended use for the market image drug product and transferred to the quality control laboratory for the launch of the drug product. However, if there are any changes in the manufacturing process that have the potential to change the analytical profile of the drug substance and drug product, this validated method may need to be revalidated to ensure that it is still suitable to analyze the API or drug product for its intended purpose.[5-8]

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. Possible steps for a complete method validation are listed below.

Steps in Method Validation

1. Develop a validation protocol or operating procedure for the Validation

2. Define the application, purpose and scope of the method

3. Define the performance parameters and acceptance criteria

4. Define validation experiments

5. Verify relevant performance characteristics of equipment

6. Qualify materials, e.g. standards and reagents

7. Perform pre-validation experiments

8. Adjust method parameters or/and acceptance criteria if necessary

9. Perform full internal (and external) validation experiments

10. Develop SOPs for executing the method in the routine

11. Define criteria for revalidation

12. Define type and frequency of system suitability tests and/or analytical quality control (AQC) checks for the routine

13. Document validation experiments and results in the validation.

 ISSN: 2250-1177 CODEN: JDDTAO

Parameters For Method Validation:

The parameters as defined by the ICH[2, 3] and by other organizations and authors are Specificity, selectivity, precision, repeatability, intermediate precision, reproducibility, accuracy, trueness, bias, linearity range, limit of detection, limit of quantitation, robustness and ruggedness.

Selectivity / Specificity

The terms *selectivity* and *specificity* are often used interchangeably. A detailed discussion of this term as defined by different organizations has been made by Vessmann [17]. Even inconsistent with ICH, the term specific generally refers to a method that produces a response for a single analyte only, while the term selective refers to a method which provides responses for a number of chemical entities that may or may not be distinguished from each other. If the response is distinguished from all other responses, the method is said to be selective. Since there are very few methods that respond to only one analyte, the term selectivity is usually more appropriate. The USP monograph [8] defines selectivity of an analytical method as its ability to measure accurately an analyte in the presence of interference, such as synthetic precursors, excipients, enantiomers and known (or likely) degradation products that may be expected to be present in the sample matrix.

Determination:-

In the case of qualitative analyses, the ability to select between compounds of closely related structure that are likely to be present should be demonstrated. This should be confirmed by obtaining positive results from samples containing the analyte, coupled with negative results from samples that do not contain the analyte and by confirming that a positive response is not obtained from materials structurally similar to or closely related to the analyte.[21]

Selectivity in liquid chromatography is obtained by choosing optimal columns and setting chromatographic conditions such as mobile phase composition, column temperature and detector wavelength. It is a difficult task in chromatography to ascertain whether the peaks within a sample chromatogram are pure or consist of more than one compound. While in the past chromatographic parameters such as mobile phase composition or the column has been modified. More recently the applications of spectroscopic detectors coupled on-line to the chromatograph have been suggested[3,5] The principles of diode-array detection in HPLC and their application and limitations to peak purity are described in the literature [19-21].

Precisions and Reproducibility

The precision of a method is the extent to which the individual test results of multiple injections of a series of standards agree. The measured standard deviation can be subdivided into three categories: repeatability, intermediate precision and reproducibility[2, 3].

Repeatability is obtained when one operator using one piece of equipment over a relatively short time-span carries out the analysis in one laboratory. At least 5 or 6 determinations of three different matrices at two or three different concentrations should be done and the relative standard deviation calculated.

Intermediate precision is a term that has been defined by ICH[2] as the long-term variability of the measurement process and is determined by comparing the results of a method run within a single laboratory over a number of weeks. A method's intermediate precision may reflect discrepancies in results obtained by different operators, from different instruments, with standards and reagents from different suppliers, with columns from different batches or a combination of these.

Objective of intermediate precision validation is to verify that in the same laboratory the method will provide the same results once the development phase is over.

Reproducibility as defined by ICH[2, 3] represents the precision obtained between laboratories. Objective is to verify that the method will provide the same results in different laboratories.

Accuracy and recovery

The accuracy of an analytical method is the extent to which test results generated by the method and the true value agree. The true value for accuracy assessment can be obtained in several ways.

Determination**:**-In case of a drug substance, accuracy may be determined by application of the analytical method to an analyte of known purity or by comparison of the results with well characterized method ,the accuracy of which has been stated or defined.[17,18]

Linearity and calibration curve

The linearity of an analytical method is its ability to elicit test results that are (directly or by means of well-defined mathematical transformations) proportional to the concentration of analytes in samples within a given range. Linearity is determined by a series of three to six injections of five or more standards whose concentrations span 80-120 percent of the expected concentration range. The response should be (directly or by means of a well-defined mathematical calculation) proportional to the concentrations of the analytes. A linear regression equation applied to the results should have an intercept not significantly different from zero. If a significant nonzero intercept is obtained, it should be demonstrated that there is no effect on the accuracy of the method.[17,18]

Range

The range of an analytical method is the interval between the upper and lower levels (including these levels) that have been demonstrated to be determined with precision, accuracy and linearity using the method as written. The range is normally expressed in the same units as the test results (e.g. percentage, parts per million) obtained by the analytical method.

The range of the method is validated by verifying that the analytical method provides acceptable precision, accuracy and linearity when applied to samples containing analyte at the extremes of the range as well as within the range.

 ISSN: 2250-1177 CODEN: JDDTAO

Limit of detection:

It is the lowest concentration of analyte in a sample that can be detected but not necessarily quantified. In chromatography the detection limit is the injected amount that results in a peak with a height at least twice or three times as high as the baseline noise level.[16]

Determination:-

the detection limit is generally determined by the analysis of samples with known concentration of analyte and by establishing the minimum level at which the analyte can be reliably detected.[21]

Limit of quantitation:

It is the minimum injected amount that gives precise measurements, in chromatography typically requiring peak heights 10 to 20 times higher than baseline noise.

Ruggedness

Ruggedness is measure of reproducibility test results under the variation in conditions normally expected from laboratory to laboratory and from analyst to analyst.[13]

The Ruggedness of an analytical method is degree of reproducibility of test results obtained by the analysis of the same samples under a variety of conditions, such as; different laboratories, analysts, instruments, reagents, temperature, time etc.

Robustness

Robustness of analytical method is a measure of its capacity to remain unaffected by small but deliberate variations in method parameters and provides an indication of its reliability during normal usage.[15]

CLEANING VALIDATION

Cleaning validation is a documented process that proves the effectiveness and consistency in cleaning a pharmaceutical production equipment1. Validations of equipment cleaning procedures are mainly used in pharmaceutical industries to prevent cross contamination and adulteration of drug products hence is critically important. The prime purpose of validating a cleaning process is to ensure compliance with federal and other standard regulations. The most important benefit of conducting such a validation work is the identification and correction of potential problems previously unsuspected, which could compromise the safety, efficacy or quality of subsequent batches of drug product produced within the equipment. The objectives of equipment cleaning and cleaning validation in an Active Pharmaceutical Ingredient (API) area are same as those in pharmaceutical production area. In both these areas efforts are necessary to prevent contamination of a future batch with the previous batch material. The cleaning of 'difficult to reach' surface is one of the most important consideration in equipment cleaning validation. Equipment cleaning validation in an API facility is extremely important as cross contamination in one of the pharmaceutical dosage forms, will multiply the problem.[15-18]

Cleaning Procedures

Standard cleaning procedures for each piece of equipment and process should be prepared. It is vital that the equipment design is evaluated in detail in conjunction with the product residues which are to be removed, the available cleaning agents and cleaning techniques, when determining the optimum cleaning procedure for the equipment.[20]

Testing methods

The basic requirements of the analytical methods should have the following criteria.

1. Testing method should have the ability to detect target substances at levels consistent with the acceptance criteria.

2. Testing method should have the ability to detect target substances in the presence of other materials that may also be present in the sample.

3. The testing analytical method should include a calculation to convert the amount of residue detected in the sample to 100% if the recovery data generated indicates a recovery outside

the allowed range.[18-20]

Analyzing cleaning validation samples

There are many analytical techniques available that can be used in cleaning validation. But choosing the appropriate analytical tool depends on a variety of factors. The most important factor is to determine the specifications or parameters to be measured. The limit should always be established prior to the selection of the analytical tool.[19]

Specific and non-specific methods

A specific method detects unique compounds in the presence of potential contaminants. Ex: HPLC. Non-specific methods are those methods that detect any compound that produces a certain response

Ex: Total Organic Carbon (TOC), pH and conductivity.[19,20]

IMPORTANCE OF VALIDATION

The most compelling reasons to optimize and validate pharmaceutical productions and supporting processes are quality assurance and cost reduction .the basic principles of quality assurance has as their goal and the production of articles that are fit for there intended use.[10] These principles are Quality, safety, and effectiveness must be designed and built in to the product, quality cannot be inspected or tested in the finished products and each step of the manufacturing process must be controlled to maximize the probability that the finished product meets all quality and design specification. The relationship of quality assurance and process validation goes well beyond the responsibility of any quality assurance functions, nevertheless it is fair to say that process validation is a quality assurance tool because it is establishes a quality standard for the specific process.

CONCLUSION:

Quality control is the part of GMP, it is concerned with the sampling specification, testing and with organization documentation and release procedures. Where as assurance

of quality is derived from careful attention to a number of factors including selection of quality materials, equipments, adequate product, process design ,selection of approved vendors, proper GMP inspections , employee training ,technical audit, critical evaluation of market complaints, in-process control of processes, and end product testing. 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 .In addition timely and appropriate validation improves quality assurance ,reduces cost by process optimization ,enables more effective and rapid trouble shooting ,shortens lead time leading to low inventories ,empowers all employees to control their processes and to improve them ,enables better system control ,maintains, and improves a high degree of assurance that specific process will consistently produce a product meetings its predetermined specifications and quality characteristics.

ACKNOWLEDGEMENT:

The authors are thankful to Director, Grd(Pg)Imt, Dept. of Pharmacy, Dr. Lakshmayya for his encouragement for carrying out this review work.

CONFLICT OF INTEREST:

The authors have no conflict in the publication of this review work. All the authors are under mutual understanding

REFERENCES

1. Agalloco J. Validation: an unconventional review and reinvention, PDA J Pharm Sci Tech, 1995, 49, 175–179.
2. Aleem H, Zhao Y, Lord S, McCarthy T and Sharratt P. Pharmaceutical process validation: an overview, J Proc Mech Eng, 2003, 217, 141-151.
3. Lambert J. Validation Guidelines For Pharmaceutical Dosage Forms. Health Canada / Health Products and Food Branch Inspectorate, 2004, 7-15.
4. Lingnau J. Optimization and Validation of Manufacturing Processes, Drug Dev Ind Pharm, 1989, 15, 1029-1046.
5. Nash R. A. and Wachter A. H. Pharmaceutical Process Validation An International Third Edition. Revised and Expanded, Marcel Dekkar, Inc., New York; 2003,129, P. 760-792.
6. Ramamurthy, M. and Sarvanakumar, K., The Eastern Pharmacist., 1997, XL, 476, 45-47.
7. UK Orange Guide, Guide to Good Pharmaceutical Manufacturing Practices, 1983, 10.
8. Zutshi, R. and Dagar, V, The Eastern Pharmacist., 1991, 34(401), 37-38.
9. Code of Federal Regulations, 1989, Title 21 part 211.40.
10. International Conference on Harmonization (ICH) of Technical Requirements for the Registration of Pharmaceuticals for Human Use, Validation of analytical procedures, ICH-Q2A, Geneva 1995.
11. International Conference on Harmonization (ICH) of Technical Requirements for the Registration of Pharmaceuticals for Human Use, Validation of analytical procedures: Methodology, ICH-Q2B, Geneva 1996.
12. US EPA, Guidance for methods development and methods validation for the Resource Conservation and Recovery Act (RCRA) Program, Washington,1995.
13. US FDA Technical Review Guide: Validation of Chromatographic Methods, Center for Drug Evaluation and Research (CDER), Rockville, MD, 1993.
14. US FDA, General principles of validation, Rockville, MD, Center for Drug Evaluation and Research (CDER), May 1987.
15. Guidance for Industry; Process Validation: General Principles and Practices 2008.
16. Robert A .Nash, Alfred H. Wachter, Pharmaceutical Process Validation, Vol.129, Third Edition, Marcel Dekker, Inc, New York, 2003.
17. James Agalloco, Frederick J. Carleton, Validation of Pharmaceutical Processes, Third Edition, Informa Healthcare USA, Inc., New York, 2008.
18. United States Pharmacopoeia and the National Formulary XXIII, 18th ed,. Rockville, MD: The United States Pharmacopoeia Convention Inc., 1995, pp 1982 – 1984.
19. Chapman GM, Amer G, Boyce C, Brower G, Green C, Hall WE, Harpaz D, Mullendore B. Proposed Validation Standard VS1: Non-aseptic Pharmaceutical Processes. J Val Technol 2000, 6, 502-20.
20. LeBlane DA. Establishing scientifically justified acceptance criteria for cleaning validation of finished drug product. Pharm Technol, 1998, 23(10), 136-48.
21. WHO Expert Committee on Specifications for Pharmaceutical Preparations, 34th Report. WHO Technical Report Series no. 863, Annex 6, Geneva: WHO, 1966, P. 80-96.

