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# Pharmaceutical Validation–A Review

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## Abstract

Validation is documented evidence that provides high degree of assurance. Validation has become one of the pharmaceutical industries most recognized subjects. This article provides brief introduction about the pharmaceutical validation & its importance. Quality is always an imperative prerequisite when we consider product. Therefore, drugs must be manufactured to the highest quality levels. QA techniques must be used to build the quality in to the product at every step and not just tested for at the end it is an important technique for providing the quality of the product. In this article we discus about the types of validation, cleaning & analytical method validation, protocols, VMP etc. Manufacturing and cleaning equipment must be designed for effective and consistent cleaning to avoid cross contamination and the cleaning processes must be verified as effective. Validation is the process which is used to conform that the analytical procedure employed for a specific test is suitable for intended use.

**Keywords:** validation, cleaning validation, analytical method validation, protocol, VMF, vendor qualification etc.

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## 1. Introduction

**Validation:**
The process of providing documented evidences, that provides high degree of assurance a result with pre determine acceptance criteria.

**Importance of validation:**

a. Increased throughput
b. More rapid and reliable start up of new equipment
c. Easier scale-up from development work

d. More rapid automation
e. Reduction in utility cost

**Types of validation:**

a. Retrospective validation
b. Prospective validation
c. Concurrent validation
d. Revalidation

**1. Retrospective validation:**

Establishing documented evidence prior to process implementation that a system does what proposed to do based on preplanned protocols. This approach to validation is normally undertaken whenever the process for a new formula must be validated before routine pharmaceutical production commences. In fact, validation of a process by this approach often leads to transfer of the manufacturing process from the development function to production the retrospective validation is used for facilities, processes, and process controls in operation use that have not undergone a formally documented validation process.

**2. Prospective validation:**

It is used for facilities, processes, and process controls in operation use that have not undergone a formally documented validation process. Validation conducted prior to distribution either of a new product, or a product made under a revised manufacturing process. Validation is completed and the results are approved prior to any product release establishing documented evidence prior to process implementation that a system does what it proposed to do based on pre-planned protocols. Each prospective validation step will be described in qualification/validatuion documents.

**3. Concurrent validation:**

It is a combination of retrospective and prospective validation. Performed against an approved protocol but product is released on a lot-by-lot basis. Usually used on an existing product not previously validated or insufficiently validated. Concurrent validation is used for establishing documented evidence that a facility & processes do what they purport to do, based on information generated during actual imputation of the process.

**4. Revalidation**:

It means repeating the original validation effort or any part of it, and includes investigative review of existing performance data. This approach is essential to maintain the validated status of the plant, equipment, manufacturing processes and computer systems. Possible reasons for starting the revalidation process include:

- The transfer of a product from one plant to another.
- The necessity of periodic checking of the validation results.
- Significant increase or decrease in batch size.
- The scope of revalidation procedures depends on the extent of the changes and the effect upon the product.

## 2. Cleaning Validation

Cleaning validation is the process of assuring that cleaning procedures effectively remove the residue from manufacturing equipment / facilities below a predetermined level. Cleaning validation primarily applicable to the cleaning of process manufacturig equipment in the pharmaceutical industry. The term cleaning validation is to be used to describe the analytical investigation of a cleaning procedures or cycle.

It should also explain the development of acceptance criteria, including chemical & microbial specifications, limits of detection & the selection of sampling methods.

**Objectives**:

**The reasons for validating the cleaning procedure:**

- It is a customer requirement.
- It ensures the safety and purity of the product.
- It is regularity requirement in active pharmaceutical ingredient product manufacture.
- Pharmaceutical products and API can be contaminated by other pharmaceutical products, cleaning agents & microbial contamination. The objective of the cleaning validation is to verify the effectiveness of cleaning procedure for removal of product residues, degradation products, preservatives, excipients and/ or cleaning agents as well as the control potential microbial contamination.

**Elements of Cleaning Validation**

**Establishments of acceptance criteria:**

The Cleaning Validation should demonstrate that the procedure consistently removes residues of the substance previously manufactured down to levels that are acceptable and that the cleaning procedure itself does not contribute unacceptable levels of residual materials to the equipment. The limits set should be practical, achievable and justifiable. In Active Pharmaceutical Ingredient manufacture there may be partial reactants and unwanted by-products which may not have been chemically identified. Therefore, it may be necessary to focus on by-products as

well as the principle reactant. Companies should decide on which residue(s) to quantify based on sound scientific rational.

**Advantages:**

a. Dissolves and physically removes sample
b. Adaptable to a wide variety of surfaces
c. Economical and widely available
d. May allow sampling of a defined area.
e. Applicable to active, microbial, and cleaning agent residues

**Cleaning procedure**

a. Cleaning procedures should be sufficiently detailed to remove the possibility of any inconsistencies during the cleaning process.
b. Equipment parameters to be evaluated
c. Identification of the equipment to
d. be cleaned
e. Difficult to clean areas
f. Property of materials
g. Ease of disassembly

**Residues to be cleaned**

- Cleaning limits
- Solubility's of the residues
- Length of campaigns

**Cleaning agent parameters to be evaluated**

a. normally used in the process
b. Detergents available (as a
c. general guide, minimize use of
d. Solubility properties
e. Environmental considerations.
f. Health and safety considerations

**Cleaning techniques to be evaluated**

- Manual cleaning
- CIP (Clean-in place)
- COP (clean-out-of-place)
- Semi automatic
- Automatic
- Time considerations

**Other requirements**

**Sampling Techniques**

The selection of either of these techniques must be consistent with sound scientific judgment and must support the objective of the study, which is to demonstrate that the amount of residual material in the equipment has been reduced to acceptable levels**.** There are three known sampling methods:

**a. Direct surface sampling**:

It involves the determination of the type of sampling methods used & its impact on the test data to check the interference of the sampling material with the test. Therefore, early in the validation program, it is crucial to assure the sampling medium & solvent if they are satisfactory and be readily used. Advantages of direct sampling are that, areas hardest to clean and which are reasonably, acceptable can be evaluated, leading to establishing a level of contamination or residue per given surface area.

**Limitations:**

a. An invasive technique that may introduce fibers
b. Results may be technique dependent
c. Swab material and design may inhibit recovery and specificity of the method.
d. Evaluation of large, complex and hard to reach areas difficult (e.g., crevices, pipes, valves, large

**b. Swab sampling:**

Swabbing (Or Direct Surface Sampling) Method or Swab sampling does not cover the entire equipment surface area, therefore sites must be chosen with care. It is important that, as a minimum, the swab sites represents worst case locations on the equipment and that the result is then extrapolated to account for the total product contact surface Area. The solvent used for swabbing should provide good solubility for the compound and should not encourage degradation.

**c. Rinse sampling:**

Sampling and testing of rinse samples for residual active ingredient is a commonly adopted method to evaluated cleanliness. This is a fairly convenient method in many cases and requires control over the solvent used for rinsing, the contact time and the mixing involved. The solvent should be selected based on the solubility of the active ingredient and should either simulate a subsequent batch of product or at least provide adequate solubility.

**Advantages:**

a. Adaptable to on-line monitoring
b. Easy to sample
c. Non-intrusive
d. Less technique dependent than swabs
e. Applicable for actives, cleaning agents and excipients.
f. Allows sampling of a large surface area

**Disadvantage:**

Residues or contaminant may not be soluble or may be physically occluded in the equipment. An analogy that can be used is the "dirty pot". In the evaluation of cleaning of a dirty pot, particularly with dried out residue one does not look at the rinse water to see that it is clean; one looks at the pot.

**1. Placebo Sampling Method**

Placebo sampling can be used to detect residues on equipment through the processing of a placebo batch subsequent to the cleaning process. It is appropriate for active residue, cleaning agent, particulates and microbial testing. Placebos are used primarily to demonstrate the lack of carryover to the next product. The placebo should mimic product attributes. The equipment characteristics also impact the choice of the placebo batch size.

**Advantages**

Placebo contacts the same surfaces as the product. Applicable for hard-to-reach surfaces, requires no additional sampling steps.

**Limitations**

a. Difficult to determine recovery (contaminants may not be evenly distributed in the placebo)
b. Lowers analytical specificity and inhibits detestability. Takes longer and adds expense since equipment must be cleaned after the placebo run. Placebos must be appropriate for each potential. Product Residues may not be homogenously distributed. No direct measurement of residues on product contact surfaces. The
**c.** preferred sampling method and the one considered as the most acceptable be regulatory authorities is the swabbing method.

## 3. Analytical Methods

Specific and non-specific are the two analytical methods used widely to detect any compound. The choice of using a specific or non specific method can be difficult. If a drug active is highly toxic, a specific method is always recommended. Chromatographic methods are preferred for cleaning validation studies because of their sensitivity, specificity, and ability to quantify.

**a. Specific method**

It is a method that detects a unique compound in the presence of potential contaminants.

Some examples of specific methods are high performance liquid chromatography (HPLC), Ion chromatography, Atomic absorption, Capillary electrophoresis, and other chromatographic methods.

**b. Non-specific method**

It detects any compound that produces a certain response. Some examples of non specific methods are Total Organic Carbon (TOC), pH, Titration, and conductivity. The basic requirement for the analytical method.The sensitivity of the method shall be appropriate to the calculated contamination limit. The method shall be practical and rapid, and, as much as possible use instrumentation existing in the company. The method shall be validated in accordance with ICH, USP, EP requirements. The analytical development shall include a recovery study to challenge the sampling and testing methods.

**Analytical Method Validation:**

Validation of an analytical procedure is the process by which it is established, by laboratory studies, that the performance characteristics of the procedure meet the requirements for its intended use. All analytical methods that are intended to be used for analyzing any clinical samples will need to be validated. Validation of analytical methods is an essential but time - consuming activity for most analytical development laboratories. It is therefore important to understand the requirements of method validation in more detail and the options that are available to allow for optimal utilization of analytical resources in a development laboratory.

**Why Validate Analytical Procedures**

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. 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.

**Cycle of Analytical Methods**

The analytical method validation activity is not a one - time study. This is illustrated and summarized in the life cycle of an analytical procedure in below Figure.

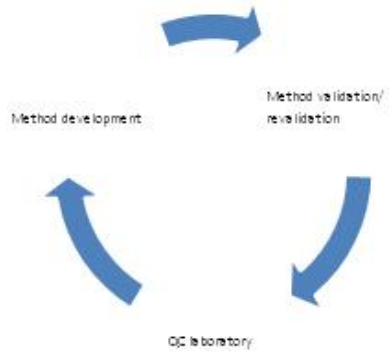


**Figure1:** Life cycle of analytical method

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.

**Analytical Method Validation Characteristics**

Typical analytical performance characteristics that should be considered in the validation

Of the types of procedures described in this chapter are listed below. Each validation characteristic is defined to ensure consistency in usage of terminology and interpretation:

1. Accuracy
2. Precision
3. Repeatability
4. Intermediate precision
5. Specificity
6. Detection limit
7. Quantitation limit
8. Linearity
9. Range
10. Robustness.

**1. Accuracy:**

The International Convention on Harmonization (ICH) defines the accuracy of an analytical procedure as the closeness of agreement between the values that are accepted either as conventional true values or an accepted reference value and the value found. For drug substance, accuracy may be defined by the application of the analytical procedure to an analyte of known purity (e.g., a reference standard). Accuracy is usually reported as percent recovery by the assay (using the proposed analytical procedure) of known added amount of analyte in the sample or as the difference between the mean and the accepted true value together with the confidence intervals. The range for the accuracy limit should be within the linear range.

Typical accuracy of the recovery of the drug substance is expected to be about 99 –101%. Typical accuracy of the recovery of the drug product is expected to be about 98 – 102%. Accuracy should be assured using a minimum of 3 concentration levels covering the specified range (eg:3 concentrations/ 3 replicates each of the total analytical procedure). The accuracy of an analytical procedure expresses the closeness of agreement between the value which is accepted either as a conventional true value or an accepted reference value and the value found.

**2. Precision**:

The precision of an analytical procedure expresses the closeness of agreement (degree of scatter) between a series of measurements obtained from multiple sampling of the same homogeneous sample under the prescribed conditions. Precision may be considered at three levels: repeatability, intermediate precision and reproducibility.

Precision should be investigated using homogeneous, authentic samples. However, if it is not possible to obtain a homogeneous sample it may be investigated using artificially prepared samples or a sample solution. The precision of an analytical procedure is usually expressed as the variance, standard deviation or coefficient of variation of a series of measurements. Precision is usually investigated at three levels: repeatability, intermediate precision, and reproducibility. For simple formulation it is important that precision be determined using authentic homogeneous samples.

**Repeatability:**

Repeatability is a measure of the precision under the same operating conditions over a short interval of time, that is, under normal operating conditions of the analytical method with the same equipment. It is sometimes referred to as intra - assay precision.

**Intermediate Precision:** Intermediate precision is defined as the variation within the same laboratory. The extent to which intermediate precision needs to be established depends on the circumstances under which the procedure is intended to be used. Typical parameters that are investigated include day - to - day variation, analyst variation, and equipment variation. Depending on the extent of the study, the use of experimental design is encouraged. Experimental design will minimize the number of experiments that need to be performed

**Reproducibility**

Reproducibility expresses the precision between laboratories (collaborative studies, usually applied to standardization of methodology).

**3. Specificity**

Specificity is the ability to assess unequivocally the analyte in the presence of components which may be expected to be present. Typically these might include impurities, degradants, matrix, etc. Lack of specificity of an individual analytical procedure may be compensated by other supporting analytical procedure(s).

This definition has the following implications:

**Identification:** to ensure the identity of an analyte.

**Purity Tests:** to ensure that all the analytical procedures performed allow an accurate statement of the content of impurities of an analyte, i.e. related substances test, heavy metals, residual solvents content, etc.

**Assay (content or potency):**

To provide an exact result which allows an accurate statement on the content or potency of the analyte in a sample.

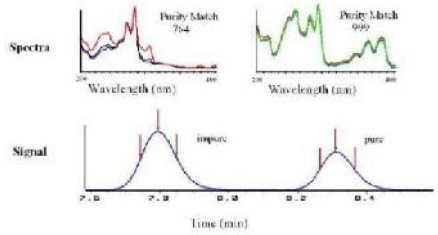


**Figure 2:** Examples of pure and impure HPLC peaks

The chromatographic signal does not indicate any impurity in either peak. Spectral evaluation, however, identifies the peak on the left as impure.

**4. Detection Limit:**

The detection limit of an individual analytical procedure is the lowest amount of analyte in a sample which can be detected but not necessarily quantitated as an exact value.

**5. Quantitation Limit**

The quantitation limit of an individual analytical procedure is the lowest amount of analyte in a sample which can be quantitatively determined with suitable precision and accuracy. The quantitation limit is a parameter of quantitative assays for low levels of compounds in sample matrices, and is used particularly for the determination of impurities and/or degradation products.

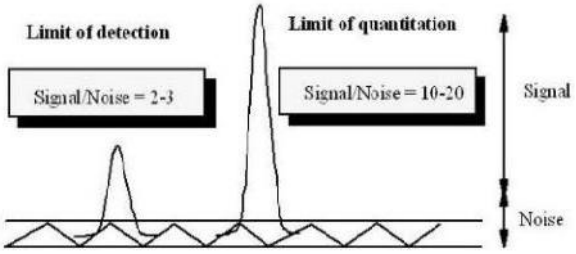


**Figure 3:** Limit of quantitation with the EURACHEM method

**6. Range**

The range of an analytical procedure is the interval between the upper and lower concentration of analyte in the sample for which it has been demonstrated that the analytical procedure has a suitable level of precision, accuracy, and linearity. The range is normally expressed in the same units as test results (e.g., percent, parts per million) obtained by the analytical procedure. For the assay of drug substance or finished drug product, it is normally recommended to have a range of 80 – 120% of the nominal concentration. For content uniformity, a normal range would cover 70 – 130% of the nominal concentration, unless a wider and more appropriate range (e.g., metered - dose inhalers) is justified. For dissolution testing, normal range is ± 20% over the specified range. If the acceptance criterion for a controlled - release product covers a region from 20% after 1 h, and up to 90% after 24 h, the validated range would be 0 – 110% of the label claim. In this case, the lowest appropriate quantifiable concentration of analyte will be used as the lowest limit as 0% is not appropriate.

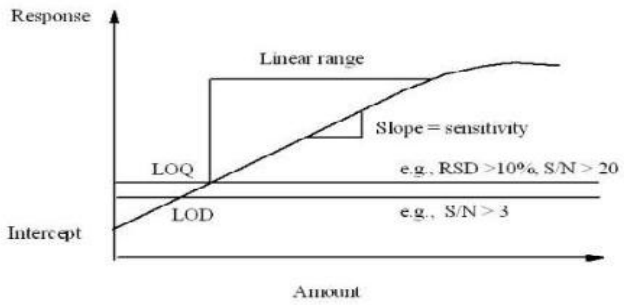


**Figure 4:** Definitions for linearity, range, LOQ, LOD

**7. Robustness**

Robustness of an analytical procedure is a measure of the analytical method to remain unaffected by small but deliberate variations in method parameters and provides an indication of its reliability during normal usage. The evaluation of robustness is normally considered during the development phase and depends on the type of procedure under study. Experimental design (e.g., fractional factorial design or Plackett –Burman design) is common and useful to investigate multiple parameters simultaneously. The result will help to identify critical parameters that will affect the performance of the method. Common method parameters that can affect the analytical procedure should be considered based on the analytical technique and properties of the samples:

1. Sample preparation
    a. Extraction time
    b. Sample solvent (pH 0.05 unit, percent organic 2% absolute)
    c. Membrane filters
    d. Sample and standard stability
2. High - performance liquid chromatography (HPLC) conditions
    a. Mobile - phase composition
    b. Column used (equivalent columns, lots and/or suppliers, age)
    c. Temperature
    d. Flow rate
3. Gas chromatography (GC) conditions
    a. Column used (lots and/or suppliers, age)
    b. Temperature
    c. Flow rate

**Process of Analytical Method Validation**

The typical process that is followed in an analytical method validation is chronologically listed below:

1. Planning and deciding on the method validation experiments
2. Writing and approval of method validation protocol
3. Execution of the method validation protocol
4. Analysis of the method validation data
5. Reporting the analytical method validation
6. Finalizing the analytical method procedure

The method validation experiments should be well planned and laid out to ensure efficient use of time and resources during execution of the method validation. The best way to ensure a well - planned validation study is to write a method validation protocol that will be reviewed and signed by the appropriate person (e.g., laboratory management and quality assurance).

The validation parameters that will be evaluated will depend on the type of method to be validated. Analytical methods that are commonly validated can be classified into three main categories: identification, testing for impurities, and assay. Execution of the method validation protocol should be carefully planned to optimize the resources and time required to complete the full validation study. For example, in the validation of an assay method, linearity and accuracy may be validated at the same time as both experiments can use the same standard solutions.

A normal validation protocol should contain the following contents at a minimum:

(a) Objective of the protocol
(b) Validation parameters that will be evaluated
(c) Acceptance criteria for all the validation parameters evaluated
(d) Details of the experiments to be performed
(e) Draft analytical procedure

The data from the method validation data should be analyzed as the data are obtained and processed to ensure a smooth flow of information. If an experimental error is detected, it should be resolved as soon as possible to reduce any impact it may have on later experiments. Analysis of the data includes visual examination of the numerical values of the data and chromatograms followed by statistical treatment of the data if required.

**Information Required In Analytical Procedure:**

The minimal information that should be included in a final analytical procedure are as follows:

(a) Rationale of the analytical procedure and description of the capability of the method. Revision of analytical procedure should include the advantages offered by the new revision.
(b) Proposed analytical procedure. This section should contain a complete description of the analytical procedure in sufficient detail to enable another analytical scientist to replicate it. The write - up should include all important operational parameters and specific instructions, for example, preparation of reagents, system suitability tests, precautions, and explicit formulas for calculation of the test results.
(c) List of permitted impurities and its levels in an impurity assay.
(d) Validation data. Either a detailed set or summary set of validation data is included.

**Vendor Qualification**

Vendor qualification is system of assuring that a supplier product is produced under controlled conditions, resulting in consistent quality conformance. Based on the principle of defect prevention, rather than defect detection and inspection, it significantly reduces the need for customer inspection.

Vendor qualification is a supplier-customer partnership and can only be successful with full involvement and agreement of both partners.

**Relationship Between Sponsor, Vendor And Supplier:**

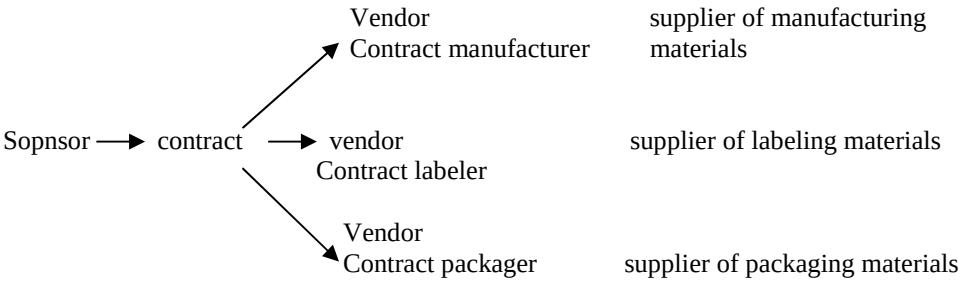


**Figure 5:** Relationship between sponsor, vendor and supplier

**Why to qualify vendors**

- Used to determine if the vendor is appropriate for the scope of work.
- Critical attributes of a partner relationship are supplier or customer commitment to a long term relationship.
- Information sharing.
- Performance measurement and feedback.
- Customer confidence in the supplier's manufacturing capability, quality, cost, and development.
- These attributes will vary depending on the status of the supplier-customer relation.

**Purpose Of Vendor Qualification And Certification:**

- The tighter specification ranges usually result in higher yields and reduced equipment downtime for the supplier, thereby providing an opportunity to reduce prices or minimize price increases. A similar situation can occur with the customer and should also result in more consistent product quality.
- Reduced testing by the customer eliminates some testing costs but more importantly can make materials available to production more quickly. This allows further inventory reduction and is also of benefit when materials are urgently required for unexpected production.
- **Regulatory aspects:** Regulatory authorities world wide including US FDA are extending the validation and GMP requirements from finished pharmaceuticals to include APIs. This is evident in the evident in the FDAs compliance guide and internationally in the guideline on GMP for pharmaceutical excipients.
- **Business aspect:** Proper validation of finished dosage form cannot be effective without consideration being given to the APIs used in the manufacture of the finished dosage form and critical parameters involved i.e., APIs.

**Key Steps Involved in The Qualification Process:**

Every finished pharmaceutical manufacturer should have a written procedure to qualify and certify an API vendor. If the vendor is not a manufacturer, then the vendor should be qualified and certified for each specific manufacturer and the procedure should include all aspects of current regulator y requirements. The specifications must be based on the testing of material from a specific manufacturer(s) and not necessarily a vendor, who may be a distributor.

**Customer teams:**

Several functions need to be involved in establishing a vendor certification process. Typically the team will include representatives from manufacturing, package engineering, purchasing and quality assurance with support, as appropriate, from other disciplines such as finance and research and development.

**Supplier selections:**

The long term intent would be to certify all suppliers but this is likely to take considerable time and effort. The initial selection of potential partners should take ‘in to account the supplier’s history in terms of quality, delivery, and support service as well as the importance of the specific material to the business. Vendor certification has a higher chance of success with a supplier who already has a high commitment to quality and customer service.

**Initial supplier contacts:** The proposed process will be discussed with the supplier.

**Process elements:**

**Supplier process:** some or all of the customer vendor certification team should visit the supplier’s plant to gain an understanding of the production process and the key elements which impact on the achievement of quality standards.

**Specifications:** A detailed review should be made of product specifications with particular reference to legal requirements (compendia, FDA, etc) and fitness for use. This latter point is likely to require a supplier understanding of the customer’s process; in this way it may the possible to relax certain less critical specification parameters while tightening or increasing the level of assurance on more critical parameters. Test methods should, where possible be identical.

**Process evaluation:** The supplier must have suitable equipment to monitor the process. This equipment must be routinely calibrated and test methods validated. Process control data for several batches, chosen at random, should be reviewed to confirm supplier compliance.

Increasingly, vendors are being requested to demonstrate that their production processes are validated, especially for the manufacture of bulk pharmaceutical chemicals.

**Process and specification changes:** The important element in the vendor certification process is the procedure for handling any changes to the process or the specification. Any proposed changes must be clearly documented, with reasons and supporting data, and be reviewed and accepted by the customer prior to introduction. Some changes may require customer evaluation and even FDA approval before acceptance. Any proposed changes to the customer’s process which could impact on the usability or performance of the supplier’s material also require prior review and agreement with the supplier. For example, if the customer was contemplating replacement of a packaging line, there would need to be discussions with the supplier of the packaging components.

**Customer inspection:**

After it has been confirmed that a supplier has a controlled process, there usually will be a period when both parties evaluate material quality and compare data. This provides the needed assurance that supplier and customer have comparable evaluation ability and minimizes future potential for disagreements that are due to test results rather than a typical product. Vendor certification provides a strong basis for the application of reduced testing by the customer. If the supplier’s process is under control, any evaluation by the customer should only have value with respect to any changes during shipment. The customer should perform audits of the supplier’s process at appropriate intervals. This can be a useful opportunity to review the entire vendor certification process and to evaluate success.

**Supplier reporting:**

since vendor certification is a partnership, it is important that both supplier and customer are kept informed of each other’s difficulties. This supplier must notify the customer of any a typical situations or process deviations prior to shipping material so that any additional testing or evaluations may be performed. The supplier should also provide

certificates of compliance or certificates of analysis for every batch formatted in a manner which is acceptable to the customer should also provide feedback to the supplier with respect to compliance with specification in use, and delivery service.

**Vendor audits:**

One critical step in vendor qualification is verification that the vendor should be in compliance with the intent of GMP. One of the problems faced by substances or excipients. There are several movements underway to develop guidelines; however, there is no official regulatory document at this time by which to measure cGMP compliance for a vendor. The person conducting the audit uses a check list developed for this purpose for two main reasons.

a. The checklist will include all areas of the audit to be covered so that nothing will be forgotten.
b. Boxes on the checklist can be marked, with brief comments that can be added by the auditor, obviating the need for much time spent observing the facility and asking plant personal questions in a dialogue.

**The following are some of the major points to be considered during audit.**

**Documentation:**

An organization that fallows quality principles must rely on its systems of documentation in order to maintain regulatory compliance. An API manufacturing operation must utilize written procedures that are followed to describe the manufacturing and control operation.

**Change control:**

It should be documented in a procedure so as to provide consideration for revalidation and additional stability studies when changes are being considered in the manufacturing operation.

This is true for both supplier and customer. Furthermore a change in an API operation can affect a dosage form in that specifications and stability may be compromised.

**Distribution records:**

An API manufacturer's documentation system must extend to distribution records so that each shipment of each lot of API product can be traced to every customer shipped lot. The documentation is especially important in the event that a lot of API product is identified as being defective after it is quality control approved and shipped to a customer so that the lot can be retrieved by the manufacturer. An API lot can be defective if it should fail to meet its predetermined specifications.

**Returned goods**

Some common reasons for the return are:

a. Customer did not order or want the material.
b. Material does not meet the customer's specifications.
c. Containers are damaged
d. Material appears contaminated with a foreign substance.

**Decertification:**

Certification results in a high level of reliance on the supplier: reduced incoming inspection, reduced inventories, higher output. Any failure by the supplier can therefore have serious consequences and may require decertification of that supplier for that material. Depending on the nature of the problem it may be possible to work with the supplier to reestablish certification, or the supplier may be relegated to a lesser status as "approved" or "preferred".

**Vendor Selection Criteria:**

a. Quality
b. Delivery
c. Performance
d. Production facilities
e. Financial position
f. Price
g. Desire for business
h. Repair service
i. Labor relation record
j. Management and organization
k. Operating control
l. Packaging ability

**Validation Master Plan**

The validation master plan is a document that describes how the validation program will be executed in a facility. Even though it is not mandatory it is the document that outlines the principles involved in the qualification of a facility, defines the areas and systems to be validated and to provide a written program for achieving and maintaining a qualified facility with validated processes. It is the foundation for the validation program and should include process validation, facility and utility qualification and validation, equipment qualification, cleaning and

computer validation. The regulations also set out an expectation that the different parts of the production process are well defined and controlled, such that the results of that production will not substantially change over time.

Validation master plan also referenced as VMP is one of the key documents in the GMP regulated pharmaceutical industry. A validation master plan drives a structured approach to validation products that will allow you to address many problems before they become crises. A VMP outlines the principles involved in the qualification of a facility, defining the areas and systems to be validated and provides a written program for achieving and maintaining a qualified facility with validated processes. The VMP is the foundation for the validation program and should include process validation, facility and utility qualification and validation, equipment qualification, cleaning computer validation.It is document pertaining to the whole facility that describes which EQ ,systems, methods and processes will be validated and when they will be validated. Provide the format required for each particular validation document (IQ, OQ, PQ, for EQ and systems; process validation, analytical assay validation).

a. Indicate what information is to be contained within each document
b. Indicate why and when revalidations will be performe.
c. Enables overview of entire validation project

**List to be validated with planning schedule as its heart**

a. A validation master plan is a document that summarizes the company's overall philosophy, intentions and approaches to be used for establishing performance adequacy.
b. The validation master plan should be agreed upon by management.
c. Validation in general requires meticulous preparation and careful planning of the various steps in the process. In addition, all work should be carried out in a structured way according to formally authorized standard operating procedures.
d. All observations must be documented and where possible must be recorded as actual numerical results. s
e. It should provide an overview of the entire validation operation, its organizational structure, its content and planning.
f. The main elements include the list/ inventory/ of the items to be validated and planning schedule.
g. All validation activities relating to critical technical operations, relevant to product and process controls within a firm should be included in the validation master plan.
h. It should comprise all prospective, concurrent and retrospective validations as well as re-validation.
i. The validation master plan should be a summary document and should therefore be brief, concise and clear.
j. It should not repeat information documented elsewhere but should refer to existing documents such as policy documents, SOP' s and validation protocols and reports.

**In summary, VMP should contain atleast:**

1. Validation policy
2. organizational structure
3. Summary of facilities, systems, equipment, processes to be validated
4. Documentation format for protocols and reports
5. Planning and scheduling
6. Change control
7. Training requirements.

**The Format And Contents of VMP:**

Introduction: Validation policy, scope, location, and schedule.
Organizational structure: Personnel responsibilities.
Specific process considerations: That are critical and those requiring extra attention.
List of products/ processes/ systems to be validated, summarized in a matrix format, validation approach.

a. Revalidation activities, actual status and future planning.
b. Key acceptance criteria.
c. Documentation format
d. Reference to the required SOP' s
e. Time plans of each validation project and sub-projects.

**Validation Protocol:**

a. A written plan starting how validation will be conducted, including test parameters, product characteristics, production and packaging equipment, and decision points on what constitutes acceptable test results.
b. The document should give details of critical steps of the manufacturing process that should be measured, the allowable range of variability and the manner in which the system will be tested.
c. The validation protocol provides a synopsis of what is hoped to be accomplished.

d. The protocol should list the selected process and control parameters, state the number of batches to be included in the study, and specify how the data, once assembled, will be treated for relevance.
e. The data of approval by the validation team should also be noted.
f. In the case where a protocol is altered or modified after its approval, appropriate reasoning for such a change must be documented.
g. The protocol must be prepared prior to the initiation of the study and must either

## 4. Conclusion

In this article the method validation process & minimum requirements to be included in a regulatory method, cleaning procedures, VMP, validation protocols are also discussed. The validation is an important technique in now-a-days because it provides the good quality of the products in pharmaceuticals. It is important tech in every pharmaceutical Industry. These studies are useful to conform the stability indicating analytical method development for various regulatory markets.

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