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Review Article

VALIDATION OF ANALYTICAL PROCEDURES: A COMPARISON OF ICH Vs PHARMACOPOEIA (USP) Vs FDA

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ABSTRACT
Method validation is the process used to confirm that the analytical procedure employed for a specific test is suitable for its intended use. Results from method validation can be used to judge the quality, reliability and consistency of analytical results; it is an integral part of any good analytical practice. When extended to analytical procedure, depending upon the application, it means that a method works reproducibly, when carried out by same or different persons, in same or different laboratories, using different chemicals or reagents and using different equipments at different condition or environment. So In this review article we discussed about the importance and strategy of validation of analytical procedure.

KEY WORDS: Analytical Procedures, FDA, ICH, Method Validation, Process Validation, Comparative study, Validation.

INTRODUCTION

Process validation is requirement of current Good Manufacturing Practices (GMPs) for finished pharmaceuticals and of GMP regulations for medical devices and therefore applies to the manufacture of both drug product and medical devices.

The validity of a specific method should be demonstrated in laboratory experiments using samples or standards that are similar to unknown samples analyzed routinely. 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 in Table. This proposed procedure assumes that the instrument has been selected and the method has been developed. It meets criteria such as ease of use; ability to be automated and to be controlled by computer systems; costs per analysis; sample throughput; turnaround time; and environmental, health and safety requirements.

Develop a validation protocol, an operating procedure or a validation master plan for the validation

1. For a specific validation project define owners and responsibilities
2. Develop a validation project plan
3. Define the application, purpose and scope of the method
4. Define the performance parameters and acceptance criteria
5. Define validation experiments
6. Verify relevant performance characteristics of equipment
7. Qualify materials, e.g. standards and reagents for purity, accurate amounts and sufficient stability
8. Perform pre-validation experiments
9. Adjust method parameters or/and acceptance criteria if necessary
10. Perform full internal (and external) validation experiments
11. Develop SOPs for executing the method in the routine
12. Define criteria for revalidation

*According to FDA Guideline on General Principles of Process Validation, Process Validation is defined as establishing documented evidence, which provides a high degree of assurance, that specific process will consistently produce a product meeting its predetermined specifications and quality characteristics.

* According to USP General chapter <1225>, "Validation is the process of providing documented evidence that the method does what it is intended to do" or in other words the process of method validation ensures that the proposes analytical methodology is accurate, specific, reproducible and rugged for its intended use [2].

*In WHO GMP under the element "Qualification and Validation".

Validation of analytical test method, automated systems and cleaning procedure has been emphasized. It reads as under

"It is of critical importance that particular attention is paid to validation of analytical test methods, automated systems and cleaning procedure" [5]

In International pharmacopoeia the guidelines are directed primarily to the examination of chemical and physiochemical attributes, but many of the general principles are also applicable to microbiological and biological procedures.

*According to ICH Guidelines [9] Validation of an Analytical procedure is to demonstrate that it is suitable for its intended purpose.

GUIDELINE HISTORY

ICH Q2A:- Text on validation of Analytical procedures

ICH Q2B:- Guideline on validation of analytical procedures: methodology

ICH Q2R1:- Q2A+Q2B [9]

WHY VALIDATION ANALYTICAL PROCEDURE

There are many reasons for the need to validate analytical procedures [1, 3]. Among them are regulatory requirements, good science, and Quality Control requirement. The *Code of Federal Regulations* (CFR) 311.165c explicitly states that "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, specificity, and reproducibility. Finally management 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.
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. [3, 8]

STEPS IN METHOD VALIDATION

Successful acceptance of the validation parameters and performance criteria, by all parties involved, requires the cooperative efforts of several departments, including analytical development, QC, regulatory affairs and the individuals requiring the analytical data. The operating procedure or the Validation Master Plan (VMP) should clearly define the roles and responsibilities of each department involved in the validation of analytical methods.
The scope of the method and its validation criteria should be defined early in the process. These include the following questions:

- What analytes should be detected?
- What are the expected concentration levels?
- What are the sample matrices?
- Are there interfering substances expected, and, if so, should they be detected and quantified?
- Are there any specific legislative or regulatory requirements?
- Should information be qualitative or quantitative?
- What are the required detection and quantitation limits?
- What is the expected concentration range?
- What precision and accuracy is expected?
- How robust should the method be?
- Which type of equipment should be used? Is the method for one specific instrument, or should it be used by all instruments of the same type?
- Will the method be used in one specific laboratory or should it be applicable in all laboratories at one side or around the globe?
- What skills do the anticipated users of the method have?

The method's performance characteristics should be based on the intended use of the method. It is not always necessary to validate all analytical parameters that are available for a specific technique. For example, if the method is to be used for qualitative trace level analysis, there is no need to test and validate the method's limit of quantitation, or the linearity, over the full dynamic range of the equipment. Initial parameters should be chosen according to the analyst's experience and best judgment. Final parameters should be agreed between the lab or analytical chemist performing the validation and the lab or individual applying the method and users of the data to be generated by the method. Table gives examples of which parameters might be tested for a particular analysis task.
The scope of the method should also include the different types of equipment and the locations where the method will be run. For example, if the method is to be run on a specific instrument in a specific laboratory, there is no need to use instruments from other vendors or to include other laboratories in the validation experiments. In this way, the experiments can be limited to what is really necessary.

Table: Validation parameters for specific tasks

	Major compounds	Major compounds and traces	Traces	Traces
	quantitative	quantitative	qualitative	qualitative
limit of detection	no	no	yes	no
limit of quantitation	no	yes	no	yes
Linearity	yes	yes	no	yes
Range	yes	yes	no	no
Precision	yes	yes	no	yes
Accuracy	yes	yes	no	yes
specificity	yes	yes	yes	yes
ruggedness	yes	yes	no	may be

Types of Analytical Procedures to be Validated

There are 3 types of analytical procedure: [1, 3, and 6]

- Regulatory analytical procedures
- Alternative analytical procedures
- Stability indicating assay

Regulatory analysis procedures are those procedures which are official in compendia of standards recognized by legislation of country.
Alternative analytical procedures are alternative procedures for regulatory analytical procedures. Generally pharmacopoeia state alternative method can be used provided their performance is equivalent or more then pharmacopoeial analytical procedure.
Stability indicating assay is a validated quantitative method that can detect changes with time in particular properties of drug substance and drug product. It accurately measure the active ingredient without interference from degradation products, process impurities excipients or other potential impurities.

Validation of analytical procedure is directed to the four common types of analytical procedures:

- Identification tests
- Quantitative test for impurities content
- Limit test for the control of impurities
- Quantitative test of the active moiety in samples of drugs substance or drug product.

Validation characteristics which should be considered are:

1. Accuracy
2. Precision
2.1 Repeatability
2.2 Intermediate precision
3. Specificity
4. Limit of Detection
5. Limit of Quantification
6. Range
7. Linearity [6]

The degree of revalidation required depends on the nature of the changes.

COMPARISON:

According to FDA Guidelines

1. Accuracy
2. Precision
3. Repeatability
4. Injection repeatability
5. Analysis repeatability
6. Intermediate precision
7. Specificity/selectivity
8. Linearity
9. Range
10. Reproducibility
11. Limit of detection
12. Limit of quantification
13. Robustness
14. Sample solution stability
15. System suitability specifications and tests [2]

According to Pharmacopoeia (USP)

1. Accuracy
2. Precision
3. Specificity
4. Limit of detection
5. Limit of quantification
6. Range and linearity
7. Ruggedness
8. Robustness

According to ICH:

1. Accuracy
2. Precision
3. Repeatability
4. Intermediate precision
5. Specificity
6. Limit of detection
7. Limit of quantification
8. Range
9. Linearity
10. System suitability
11. Robustness [9]

ICH ELEMENTS REQUIRED FOR VALIDATION

Analytical performance parameters	identification	Impurity testing Quantitative	Limit tests	Assay
Accuracy	No	Yes	No	Yes
Precision				
Repeatability	No	Yes	No	Yes
Intermediate precision	No	Yes	No	Yes
Specificity	Yes	Yes	Yes	Yes
LOD	No	Yes	Yes	No
LOQ	No	Yes	No	No
Linearity	Yes	Yes	No	Yes
Range	Yes	Yes	No	Yes

JAPAN PHARMACOPOEIA ELEMENTS REQUIRED FOR VALIDATION

Validation characteristics/ type Of test	Identification	Impurity testing Quantitative	Limit tests	Assay
Accuracy	No	Yes	No	Yes
Precision				
Repeatability	No	Yes	No	Yes
Intermediateprecision	No	No*	No	No*
Reproducibility	No	No*	No	Yes*
Specificity	Yes	Yes	Yes	Yes
LOD	No	No	Yes	No
LOQ	No	Yes	No	No
Linearity	No	Yes	No	Yes
Range	No	Yes	No	Yes

USP ELEMENTS REQUIRED FOR VALIDATION

Analytical performance parameters	Assay category I	Assay category II Quantitative	Limit tests	Assay category III	Assay category IV
Accuracy	Yes	Yes	*	*	No
Precision	Yes	Yes	No	Yes	No
Specificity	Yes	Yes	Yes	*	Yes
DL	No	No	Yes	*	No
QL	No	Yes	No	*	No
Linearity	Yes	Yes	No	*	No
Range	Yes	Yes	*	*	No

COMPARISON OF ANALYTICAL PARAMETERS REQUIRED FOR VALIDATION

USP General chapter <1225>	ICH Q2A Guidelines	FDA Reviewer Guidance
Accuracy	Accuracy	Accuracy
Precision	Precision	Precision
No	Repeatability	Repeatability Injection analysis
No	Intermediate precision	Intermediate precision
No	No	Reproducibility
Specificity	Specificity	Specificity/selectivity
Detection limit	Detection limit	Detection limit
Quantiation limit	Quantiation limit	Quantiation limit
Linearity	Linearity	Linearity
Ruggedness	No	No
Robustness	Robustness	Robustness
System suitability (discussed separately in USP 23 general chapter <621>	System suitability	System suitability Sample solution stability

CONCLUSION

In this article the method validation process and minimum requirements to be included in a regulatory method are also discussed. Also a comparison between various parameters has been made i.e. in ICH, (USP) pharmacopoeia, & FDA and table has been drawn from those observations. In this article, it summarizes the validation parameters that are required according to the requirements. The paradigm shift under cGMP in the 21st century that requires the bench-level scientist to have the scientific and technical understanding, product knowledge, process knowledge, and assessment abilities to appropriately execute the quality function of analytical method validation.

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