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Validation of methods – but the right way

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Introduction

Validaton of a method is required whenever it must be ensured that the analytical result can be determined with consistent precision and accuracy over a long period of time and with independent sample specimens. This requirement is found in many areas of daily life, but is particularly important in the analysis of raw materials, excipients and final products of the pharmaceutical industry as well as in the analysis of residues in food.

The correct approach to validations is a delicate topic for many customers and often associated with many questions. Here, we try to answer the most frequently asked questions.

Validation standard: ISO vs. GMP

The acceptance criteria for validation are slightly different in the world of ISO accreditation (ISO = International Organisation for Standardisation) than in the world of GMP (GMP = Good Manufacturing Practice). According to ISO 17025, the laboratory has to prove that the analytical method they have chosen meets the customer's requirements, i.e. that it shows sufficient performance[1].

The GMP guideline, on the other hand, aims to ensure that the analytical methods used meet the current safety, quality and efficacy requirements of national and international competent authorities and are therefore independent of the client's requirements. The protection of the patient (whether animal or human) is top priority[2].

Furthermore, the two quality standards differ in the following: Within the framework of ISO accreditation, a matrix-specific validation is sufficient to demonstrate the performance of the method. For a GMP-compliant validation, a product-specific validation must be performed in each case. The difference is illustrated by the following example (Fig. 1):

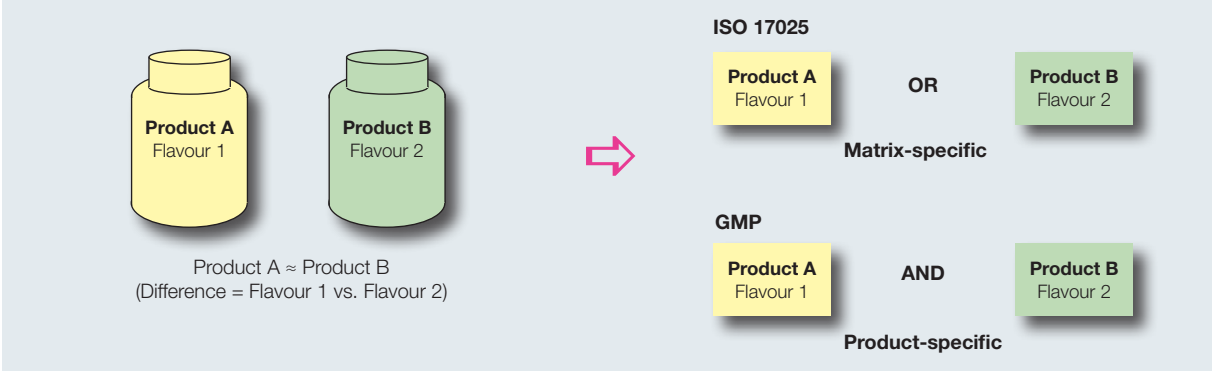
- Product A and product B have an almost identical composition and dosage form; they only differ in the flavouring agent used.
- For an ISO-compliant analysis, it is sufficient if the method has been validated with product A. Since product A and B are composed of the same matrix, no renewed validation is necessary for product B.
- For a GMP-compliant analysis, it must be shown for both product A and product B that the method meets the validation criteria, thus both products need to be validated.

Extent of a validation

The extent of a validation depends on the area of application of the method, i.e., whether one wants to determine the assay of an active ingredient in a sample, or whether one wants to know which pesticides are detectable in a vegetable. Analysis methods can roughly be divided into four main categories[3]:

- Quantitative tests for active substance content
- Quantitative tests for impurity content
- Limit tests to control impurities
- Identification tests

Figure 1: Difference between validation according to ISO 17025 and GMP



Of course, there are other tests that cannot be classified into these categories, but for which a validation might be required as well.

Once the analysis has been classified into one of these categories, the parameters to be validated are determined based on the scope of application. Not all parameters are necessary or equally relevant for all analyses. Suggestions as to which parameters should be tested for which category can be found in both the ICH Guideline[3] and the USP[4]. With a few exceptions, the suggestions are consistent. Table 1 provides a simplified overview (no claim to completeness) of the validation parameters. It can be used as a guideline for planning the extent of a method validation.

As for many things in life, several roads lead to Rome. The same is true for validations, and testing of the various validation parameters can be done in different ways. For example, one can assess the specificity of an assay determination by titration by comparing the consumption in a sample and blank analysis. For the determination of impurities by LC, one would check, among other things, whether peaks appear in the chromatogram of the placebo in the range of the analytes under investigation. Thus, there exists a certain level of freedom as long as the correct and required criteria are tested.

Before starting the validation, it is important that all the parameters to be tested as well as associated acceptance criteria are defined. This is done within the framework of a validation protocol. After the experimental determination of the previously defined validation parameters, the results are finally summarized in a corresponding report. Both documents are released at least by the laboratory performing the validation. In case of GMP, a release by the customer is also mandatory[5].

But what exactly do the different parameters signify? For a better understanding, the definitions and explanations of some relevant terms are listed in Table 2.

Aside from the methods described above, there are of course further methods that do not need to be validated because they are based on purely physical measurements. Since direct test results are generated in these cases, the use of calibrated equipment is mandatory and sufficient to confirm the validity of the result. The analysts must also be appropriately trained in the correct use of the equipment.

Table 1: Overview of common validation parameters according to ICH[3] and USP[4]

ICH category	**Quantitative tests for active substance content**		**Quantitative tests for impurity content**		**Limit tests to control impurities**		**-**		**Identification tests**	
USP category	**Category I**		**Category II Quantitative**		**Category II Limit tests**		**Category III**		**Category IV**	
	USP	ICH	USP	ICH	USP	ICH	USP	ICH	USP	ICH
Specificity/ Selectivity	•	•	•	•	•	•	1)		•	•
Accuracy	•	•	•	•	1)		1)			
Precision	•	•	•	•			•			
Linearity	•	•	•	•			1)			
Measuring range	•	•	•	•	1)		1)			
Limit of detection			1)		•	•	1)			
Limit of quantification			•	•			1)			
Robustness	•	•	•	•	•	•				

1) May be required, depending on analysis method.

Something has changed – now what?

If changes are made to either the product or the analytical method, a risk-based assessment has to be performed in each case to evaluate what impact these changes might have on the validity of the method. These considerations are necessary regardless of the underlying quality standard. For example, if chromatographic conditions are adjusted, this may have a significant impact on the detection of the analytes of interest. In this case, a re-validation is necessary and important to ensure the continued functionality of the method. Depending on the scope of the changes, a complete re-validation of the method is not always necessary; it might be sufficient to check only individual parameters. It is recommended to document within a risk assessment which parameters are to be re-validated or not and why.

Public methods

If the applied analytical method originates from a publicly available source and is implemented without any changes, a full validation of the method is not necessary. The methods have been validated as part of the publication / implementation. In these cases, verification is usually sufficient, i.e. the laboratory demonstrates that it is able to carry out the public method while complying to the appropriate performance criteria. Thus, the scope of work is reduced by some parameters. In general, pharmacopoeias (Ph. Eur., USP-NF, Ph. Helv., DAB etc.) are accepted as public methods, as well as ISO norms, methods from an authority (EU, BAFU etc.)[6] or also validated methods of an analytical kit (e.g., ELISA test)[7].
For so-called "basic compendial procedures", which are a defined selection of simple tests described in the pharmacopoeia, no verification is required according to the USP, provided they are routinely used. In such cases, the laboratory has already demonstrated that it is able to perform the tests with appropriate precision and accuracy. These simple tests include, among others, the determination of loss on drying, loss on ignition, acid value or pH value[8].

Validation in microbiology

Analyses for microbiological contaminations are usually carried out according to already validated public methods (e.g., Ph. Eur. 20612, USP <61> or ISO 16212). As mentioned above, the publicly available methods are considered validated. Thus, only a product-specific verification needs to be performed for implementation. In the case of pharmacopoeias, the corresponding general chapters already specify the acceptance criteria to be applied[11], [12].

Table 2: Definition of validation parameters

Parameter	Definition
Specificity	Ability to unambiguously detect the analyte in the presence of other expected components (e.g., matrix components)
Selectivity	Ability to detect and distinguish between multiple analytes simultaneously
Accuracy	Ability to determine the true value of the analyte in the sample
Precision	Determination of the variation of the measured value on the basis of repeated analysis of several portions obtained from a homogeneous sample
Linearity	Determination of the dependency of the measured signal on the measured variable
Measuring range	Concentration range within which quantitative statements about the analyte are possible
Limit of determination	Smallest concentration at which a qualitative statement about the analyte is still possible
Limit of quantification	Smallest concentration at which a quantitative statement about the analyte is still possible
Robustness	Determination of the effects of deliberate method variations (i.e., realistic variations in routine operation) on the method performance

From one laboratory to another

Not all methods stem from public sources or have been developed in-house. It is also possible that other companies (manufacturing sites or analytical laboratories) develop specific methods for the analysis of their products. If these methods have already been validated, a transfer of the method from the original (laboratory A) to a new laboratory (laboratory B) is possible. A complete validation by laboratory B is not necessary if the following criteria are fulfilled:

- Laboratory B receives insight and access to the original validation documents
- Laboratory B demonstrates that it has the competence and ability to perform the method correctly

By accessing the original validation data, laboratory B is given the opportunity to gain insight into the method itself, its behaviour and possible problems, e.g. what is the linear range of the detector or which interfering factors need to be considered.
To demonstrate the competence of laboratory B, several approaches are applicable[9], [10]:

- Comparative testing:
  Laboratories A and B analyse samples of the same production batch (at the same time),
- Co-validation:
  Laboratory B is already part of the validation of laboratory A, the reproducibility of the results is demonstrated,
- Re-validation:
  complete or partial validation of the method by laboratory B.

For a method transfer, a protocol and report are also prepared and must be approved by both parties involved.

If laboratory B is already performing analyses for a product of similar composition and concentration of active substance or it has already implemented methods that are very similar to the method to be transferred, additional experimental work in laboratory B might be omitted. In these cases, a so-called “transfer waiver” is prepared, a risk-based documentation of why no additional laboratory work is necessary.

Conclusion

Validations are a complex topic with a high significance under both ISO 17025 and GMP. For these two quality standards, the scope of a validation hardly differs. However, the ISO standard is more customer-centered whereas the GMP standard is patient-centered. In both cases, the parameters to be tested within a validation are essentially dependent on the type of analysis, i.e. whether quantitative or qualitative tests are performed. In case of changes to either the product to be tested or the analytical method itself, it must be assessed whether these changes are covered by the original validation or a re-validation is necessary. If the method has been validated elsewhere, a method transfer might take place in order to establish it at a new location. For public methods, only a verification of the method is required with the criteria to be fulfilled being already specified in the corresponding methods. This holds true for microbiological analyses as well.

There are many factors that have to be assessed and taken into account in order to carry out an ISO- or GMP-compliant validation of an analytical method.

We will be happy to assist you with advice. Contact our customer service for your personal consultation.

References

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[6] SAS-Leitfaden zur Validierung chemisch-physikalischer Prüfverfahren und zur Abschätzung der Messunsicherheit, 324dw, 2017-11, Rev. 03

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[10] USP-NF chapter <1224>, official prior to 2013

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[12] USP-NF chapter <61>, official prior to 2013

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