What does the pharmaceutical industry really need?

The verification and validation of pharmacopoeial methods

The analytical examination of raw materials, auxiliary materials and active ingredients, from examination on receipt to approval for the market, is important for the quality of drugs. For them to be approved, it must be ensured that the necessary quality checks are carried out in accordance with regulations and that they fulfil the regulatory requirements of the relevant market.

T
ests of raw materials are designed on the basis of official pharmacopoeias such as the European Pharmacopoeia (Ph. Eur.) and the United States Pharmacopoeia (USP). For drugs and active ingredients, the product-specific testing guidelines registered with the authorisation dossier are applied together with the corresponding specifications. The individual methods of analysis should be verified or validated depending on the complexity of the analysis and the type of substance under analysis. As well as clear specifications, it is also important here to take into account a risk-based analysis and a product life-cycle-based approach. The aim, which should be kept in sight at all times, is to fulfil the various quality requirements in a documented, demonstrable and constant manner. The primary task of analysis providers is to give competent support in the necessary documentation and demonstration of quality. The methods of analysis form the foundation of this support. They must provide reliable, correct and reproducible results.

Guide to the alphabet soup

ICH, FDA, USP, EMA, EP, JP, ISO – surely nobody can find their way around all those acronyms? The fact is that in order to prove the quality and safety of pharmaceutical substances, manufacturers need to deal with a constantly growing number of increasingly complex guidelines, provisions and regulations.

Which ones are mandatory and which ones are not? What determines which legislation is applicable? And what effect does this have on the verification and validation of methods of analysis?

The International Council for Harmonisation of Technical Requirements of Pharmaceuticals for Human Use (ICH) brings together regulatory authorities and the pharmaceuticals industry to discuss scientific and technical aspects of drug registration. It publishes international guidelines, including for analytical procedures. These are not mandatory from a strictly legal point of view, but they are often used as a basis when regulating analytical procedures. They are therefore regarded as an industry code, which is why many regulations issued by national authorities refer to ICH guidelines. ICH Guideline Q2(R1) (Validation of Analytical Procedures: Text and Methodology) is one of the most frequently cited.

For products manufactured for the U.S. pharmaceutical market, the relevant specifications are those of the Food and Drug Administration (FDA) – which, as the authority for the approval of food and drugs in the United States, is also responsible for worldwide compliance with the requirements defined in the USP. These are outlined in the FDA Guidance for Industry “Analytical Procedures and Methods Validation”.

Comparable requirements also apply to products for the European market. Here, the European Medicines Agency (EMA, formerly EMEA) sets the requirements for verifying and validating methods. Compliance with these specifications is checked by the competent authority in each country – Swissmedic
in the case of Switzerland – when the drugs are registered or in audits.

**Analyses compliant with Good Manufacturing Practice (GMP)**

When pharmaceutical companies appoint external laboratory service providers to carry out tests such as incoming goods checks or approval tests, a number of requirements must be fulfilled in order to meet the GMP requirements in full. As well as the quality of the service provider and a clear demarcation of responsibilities by means of a Quality Technical Agreement (QTA), it must also be ensured that the methods and processes used are appropriate for the specific analysis.

**Legal principles: verification**

Methods of analysis for testing raw materials, auxiliary materials and active ingredients that are described in pharmacopoeias in the form of monographs are deemed to be valid. The test of suitability (=verification) of monographed procedures (Verification of Compendial Procedures, USP General Chapter <1226>; General Notices, Ph. Eur.) is intended to ensure that these methods are appropriate both for the intended purpose and for the specific product. USP General Chapter <1226> calls for the suitability of a method to be tested in accordance with 21 CFR 211.194 and EU GMP Guide Part II Section 12.8.

This is intended to ensure, for example, that impurity profiles dependent on manufacture, logistics and storage do not have a negative impact on the reliability of the analysis results.

The experience of UFAG Laboratorien AG has shown this to be justified: substances with identical monographs produced by different manufacturers using different manufacturing, logistics and storage processes have been found to display different impurity profiles.

However, it is not possible to make a general statement on whether a verification is required. The decision of whether or not to carry out a verification should be made in close consultation with the service laboratory.

As a general tendency, however, the more complex an analytical procedure or sample preparation process is, the higher the probability will be that a verification will be necessary and the broader the required scope of the verification.

Risk-based considerations should also be taken into account: for example, a simple pH measurement will not usually be verified. If, however, a solution is measured in a particular case with a high protein content, for example, a verification should still be carried out on the basis of the expected matrix effects.

Complex analytical procedures such as HPLC/UHPLC must always be verified. Measurements using ICP-MS should normally also be verified due to the complex sample preparation process by digestion. This also applies to microbiological methods such as germ count determination or microbiological stability tests.

A special case where a method may need to be verified could also apply, at the customer’s request, if the transferring site of the original method validation is not available for a method transfer. If this is the case, it is possible to prove the correctness of a method of analysis by means of a method verification.

**Legal principles: validation**

For raw materials, auxiliary substances and active pharmaceutical ingredients (APIs), the analytical procedures monographed in the pharmacopoeias are essentially considered valid as long as no significant changes have been made.

If APIs or finished products that are not monographed in the corresponding pharmacopoeias are placed on the market, a method development and validation must always be carried out for the methods of analysis.

If a validation takes place, this must be done in accordance with ICH Guideline Q2(R1) and FDA specifications. The substance is tested for accuracy, repeatability, specificity, limit of quantification, linearity and robustness. These criteria are selected in accordance with the procedure used as a test of identity, content or purity or as a special method.

Here, in general and in addition to the basic requirements set out, the scope of the validation work follows a risk-based approach. The additional customer requirements to be met must also be checked in individual cases here.

The validation can be done on commission by a service laboratory or by the producer. In the latter case, if the analysis is to be outsourced and GMP conformity is to be confirmed, a method transfer must be carried out. The scope and execution of this method transfer is defined in close collaboration with the client.
In preparation: USP General Chapter <1220> (The Analytical Procedure Lifecycle)

In early 2015, the USP General Chapter <1225> was revised and a section on the lifecycle management of analytical methods was incorporated. In mid-2016, the USP announced the new General Chapter <1220> “The Analytical Procedure Lifecycle”.

In future, this chapter could set additional requirements for the establishment of analytical methods. Various key elements can be called for more explicitly here:

- “Procedure Design, Development, and Understanding”
- “Procedure Performance Qualification”
- “Implementation and Continued Procedure Performance Verification”

In future, this could ensure that analytical methods are developed with even more care in order to meet the “Analytical Target Profile” (ATP). Approaches from “Quality by Design” are intended to ensure the robustness of the methods.

Even after successful validation and implementation in routine use, it may be advisable to monitor these methods in order to ensure that they remain appropriate for the intended application. For example, trend analyses may be used to document the performance of methods of analysis to prove that the procedure shows the necessary reliability. This allows the need for the optimisation and possible revalidation of all or part of the analytical procedure to be estimated if need be. In addition, new information and risk assessments during the commercial life of a product may require the development and validation of a new or improved analytical procedure.

How much work is normally required for a verification or validation?

Before carrying out the first analyses, new customers must sign a Quality Technical Agreement (QTA). Using the template provided free of charge by UFAG Laboratorien, this administrative step can be completed very quickly. A verification or validation plan is then drawn up in close collaboration with the customer. This is based on the requirements of the relevant pharmacopoeias and the ICH guidelines.

Example pH-Value: For simple tests a verification is often not necessary.

«Unfortunately, the customer often does not set aside enough time to develop a method fully and is then surprised when validation takes up a lot of time.»

Once the scope of the verification or validation work has been settled, work in the laboratory can begin. The evaluation of the validation or verification is documented in a report. As soon as this has been successfully completed, the approval testing of samples can begin.

As a rule, 80% of effort is spent on development and around 20% on its verification and validation. “Unfortunately, the customer often does not set aside enough time to develop a method fully and is then surprised when validation takes up a lot of time,” says Alexander Ahnen, Head of Quality Management. “The analysis is often executed relatively quickly, since 30 provisions generally only require a few days’ work. But the evaluation can easily take two weeks. For customers, this often means that 4–6 weeks can go by from project start to the successful completion of a validation.”

The extent of the effort required for a verification depends on the complexity of the method and the product. An estimation of risk is recommended to allow the test parameters and the test effort to be selected appropriately. Certain simple tests, such as loss on drying, residue on ignition or pH, do not normally require verification. An exception to this is when the pharmacopoeia indicates that the procedure is not suitable for a particular product.

State-of-the-art analysis

The specialists at UFAG Laboratori en AG will be happy to clarify whether your particular case requires a verification or a validation. Not only do we boast a first-class infrastructure and laboratories employing state-of-the-art technology and techniques, we also employ highly trained and competent experts that are always up to date with the most recent legal requirements and standards. UFAG Laboratorien AG also provides competent, reliable support in preparing for your next official inspection.

Get in touch with us today!

Contact:
UFAG Laboratorien AG
6210 Sursee
Switzerland
Telephone +41 58 434 43 00
info@ufag-laboratorien.ch
www.ufag-laboratorien.ch