EP Chapter 5.26 IMPLEMENTATION OF ANALYTICAL METHODS AND COMPARISON WITH USP

Pavia 2023, November 17 – E. Imbriani

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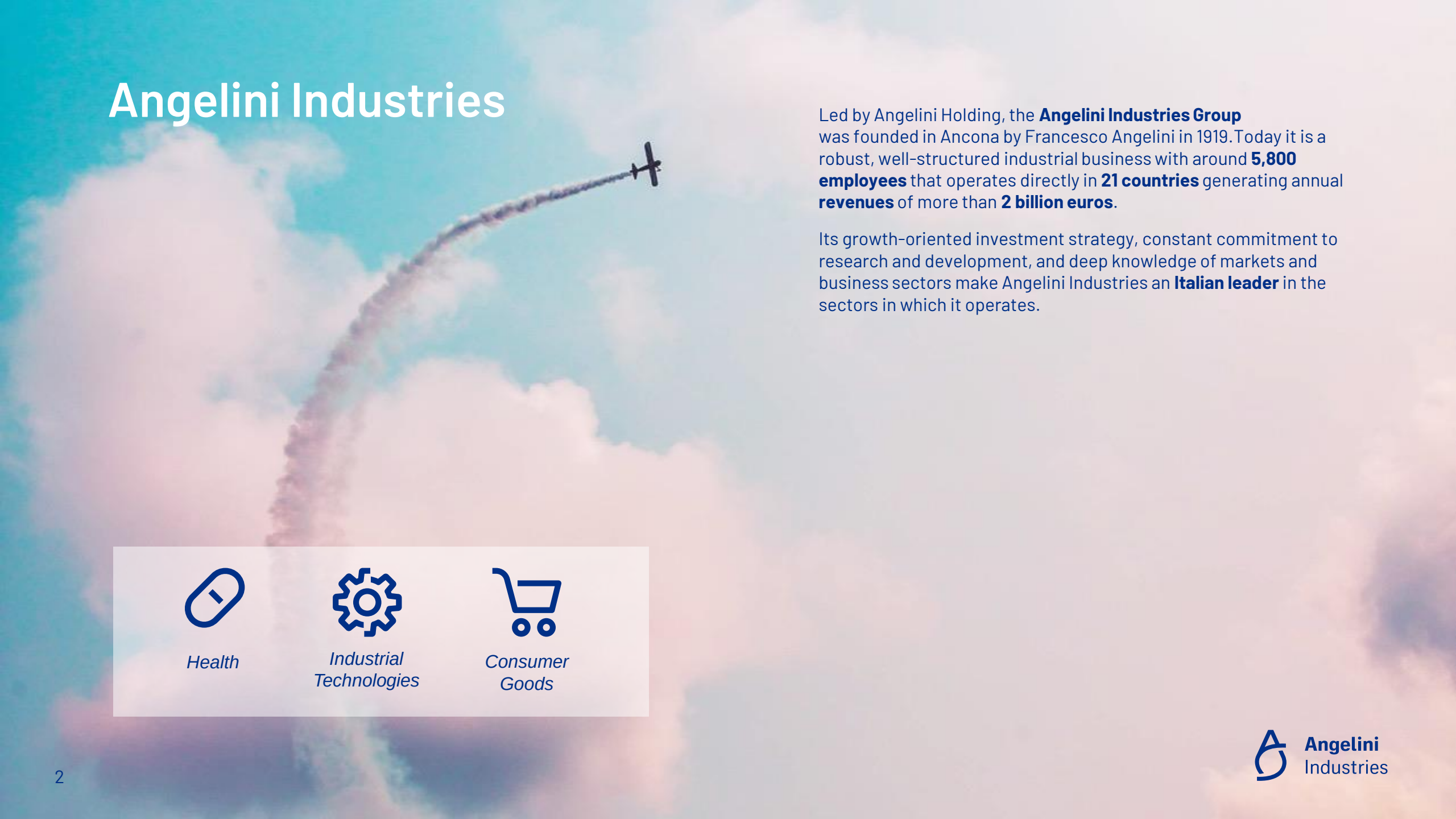

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Its growth-oriented investment strategy, constant commitment to research and development, and deep knowledge of markets and business sectors make Angelini Industries an **Italian leader** in the sectors in which it operates.

Health

Industrial Technologies

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who we are

Started more than **100 years ago** as a local pharmaceutical laboratory, Angelini Pharma is the pharmaceutical Company of Angelini Industries, grown into a leading international player in healthcare.

We are an integrated pharma company with extensive **R&D programs**, **world class manufacturing** and robust **commercial capabilities**.

We are committed to help patients fighting diseases with a focus on **Mental Health**, **Epilepsy** and **Consumer Healthcare**.

EP Chapter 5.26 implementation of Pharmacopoeial procedures and comparison with USP

Summary

- Analytical methods & Compendial monograph
- Verification vs Validation
- EP Chapter 5.26 Implementation of Pharmacopoeial Procedures
- USP <1226> Verification of Compendial Procedure

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Analytical methods & Compendial Monograph

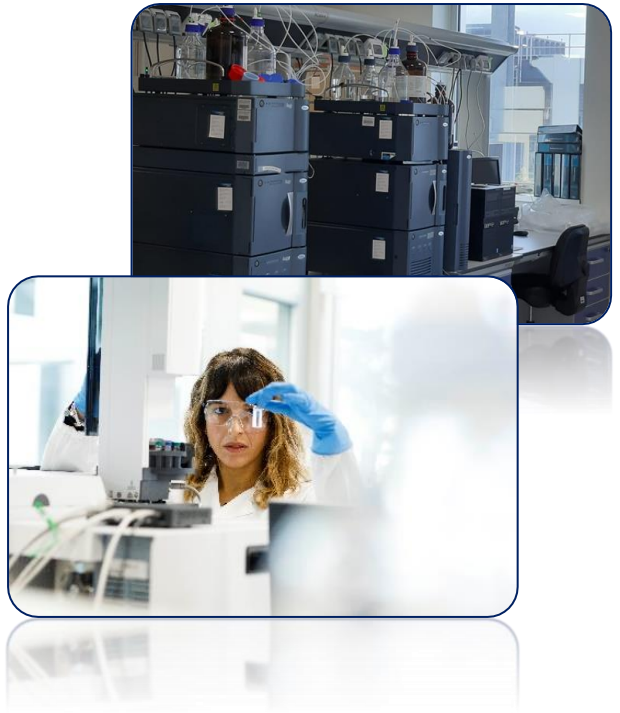
What is a an **analytical method**?

Analytical method is used to determine a chemical or physical property of a chemical substance, chemical element, or mixture.

What is a **compendial method/monograph**?

Standard protocols of analysis , reported in a Pharmacopea, for most API and finish product used in pharmaceutical manufacturing.

Compendial monograph (pharmacopeial) tests are standardized methods and specification testing for pharmaceutical raw materials (API) and finished products.



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Verification vs Validation

The compendial methods need to be verified under actual conditions of use in order to confirm the suitability of the laboratory.

Verification → capability of performing the analysis with an acceptable level of performance.

The non-compendial methods need to be validated to demonstrate that an analytical procedure is suitable for its intended purpose.

Validation → assessment, for newly developed and implemented methods, of parameters such as:

- Specificity
- Linearity and Range
- Accuracy
- Precision (repeatability, intermediate precision, reproducibility)
- Limit of Quantitation/Detection

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EP Chapter 5.26 implementation of Pharmacopoeial procedures

(EP 5.26 abstract)

This general chapter provides guidance on setting up an approach for the implementation of analytical procedures given in monographs of the Ph. Eur. (or 'pharmacopoeial procedures' hereinafter).

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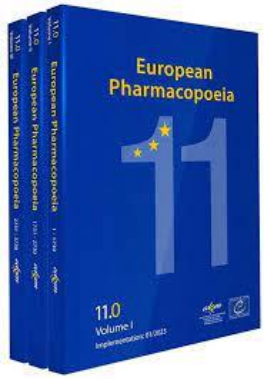
*The term "**implementation**" is used to describe the overall activities performed, whereas "**verification**" is used exclusively to refer to the experimental activities.*



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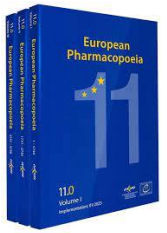
EP Chapter 5.26 implementation of Pharmacopoeial procedures



(EP 5.26 abstract)

IMPLEMENTATION PROCESS

As the first step of the implementation process, an assessment is performed prior to the first use of the pharmacopoeial procedure in the implementing laboratory. The purpose of this ***assessment*** *is not to evaluate the intrinsic capability of the procedure, but* ***to determine whether there are any factors*** *associated with the complexity of the procedure and the actual conditions of its use in the implementing laboratory* ***that may affect the performance of the procedure****.*

If such factors are identified, an experimental verification is the second step to evaluate the ***analytical procedure performance characteristics (APPCs)****, such as accuracy and precision, that are considered relevant.*

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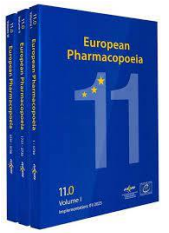

(EP 5.26 abstract)

PHARMACOPOEIAL PROCEDURE IMPLEMENTATION ASSESSMENT

During validation, the relevant APPCs were shown to be satisfactory for the intended purpose of the pharmacopoeial procedure. ***The aim of the*** *pharmacopoeial procedure implementation* ***assessment is to identify any critical factors*** *related to the actual conditions of use in the implementing laboratory that may affect the performance of the procedure.*

Possible factors: composition of the product under test, complexity of the sample preparation, reagents/laboratory equipment required to run the procedure, laboratory environment.

If **no critical factors** are identified → the procedure may be used **without verification** experiments.

If **critical factors** are identified → the procedure may be used **performing verification** experiments.

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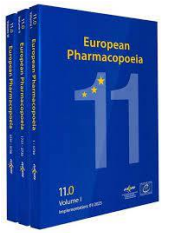

(EP 5.26 abstract)

VERIFICATION EXPERIMENTS

The purpose of the verification is to demonstrate that the implementation is feasible, i.e. that the procedure is suitable for examination of the article under test, under the actual conditions of use. If the implementation assessment identifies the need for verification experiments, relevant APPCs are assessed and verified depending on the intended use of the analytical procedure. **Table 5.26.-1** *and the section on associated points to consider provide recommendations* ***for the selection of relevant APPCs****.*

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In some cases, the tests prescribed for the purpose of verifying the ***suitability*** *of analytical procedures in an individual monograph and/or relevant general chapter can be used* ***as a partial or full verification*** *of the corresponding APPCs.*

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EP Chapter 5.26 implementation of Pharmacopoeial procedures

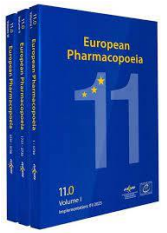

Table 5.26.-1. – Relevant APPCs to be recommended for verification based on the intended use of the procedure

Intended use / APPCs	Identification	Testing for impurities		Assay - content/potency - dissolution (measurement only)	Other quantitative tests
		Limit test	Quantitative test		
Accuracy	○	○	○	◗	◗
Precision					
- Repeatability	○	○	●	●	●
- Intermediate precision	○	○	◗	◗	◗
Specificity/Selectivity	◗	●	●	●	◗
Sensitivity	○	●	●	○	◗
Linearity	○	○	○	◗	◗
Range	○	○	○	◗	◗
Robustness	○	○	◗	◗	◗

● *signifies that this characteristic should be experimentally verified.*
◗ *signifies that this characteristic should be experimentally verified, if impacted by critical factors from the actual conditions of use in the implementing laboratory.*
○ *signifies that this characteristic is typically not relevant for purposes of verification.*

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USP <1226> Verification of compendial procedures

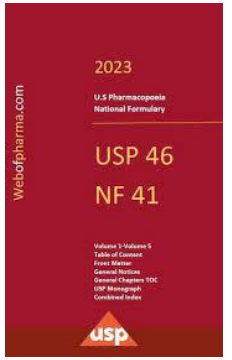
(USP <1226> abstract)

The intent of this chapter is to provide general information on the verification of compendial procedures that are being performed for the first time to yield acceptable results utilizing the personnel, equipment, and reagents available.

...

***Validation** of Compendial Procedures <1225> provides general information on characteristics that should be considered for various test categories and on the documentation that should accompany analytical procedures submitted for inclusion in USP–NF.*

***Verification** consists of assessing selected analytical performance characteristics, such as those that are described in <1225>, to generate appropriate, relevant data rather than repeating the validation process.*



No need to validate the compendial analytical procedures, but documented evidence of **suitability** should be established under **actual conditions of use**.

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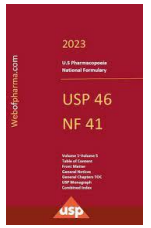
USP <1226> Verification of compendial procedures



(USP <1226> abstract)

VERIFICATION PROCESS

The verification process for compendial test procedures is the assessment of whether the procedure can be used for its intended purpose, under the actual conditions of use for a specified drug substance and/or drug product matrix.

Successful Verification → **procedure can be used** for its intended purpose in the implementing lab.

Unsuccessful Verification → develop and validate an **alternative procedure**, that may also be submitted to USP (suggestion of replacement).

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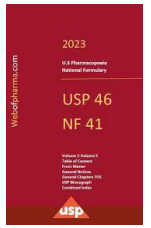
USP <1226> Verification of compendial procedures



(USP <1226> abstract)

VERIFICATION REQUIREMENTS

Verification requirements should be based on an assessment of the complexity of both the procedure and the material to which the procedure is applied.

In USP, as in EP, a complete revalidation of a compendial method is not required to verify the suitability of a procedure under actual conditions of use.

Some of the analytical parameters listed in **Validation of Compendial Procedures <1225>, Table 2** (see following slide), may be used for the verification process.

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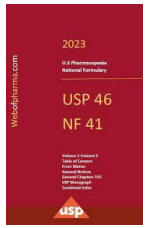
USP <1226> Verification of compendial procedures



Validation of Compendial Procedures <1225>, Table 2, may be used for the verification process.

Table 2. Data Elements Required for Validation

Analytical Performance Characteristics	Category I	Category II		Category III	Category IV
		Quantitative	Limit Tests		
Accuracy	Yes	Yes	[a]	[a]	No
Precision	Yes	Yes	No	Yes	No
Specificity	Yes	Yes	Yes	[a]	Yes
Detection limit	No	No	Yes	[a]	No
Quantitation limit	No	Yes	No	[a]	No
Linearity	Yes	Yes	No	[a]	No
Range	Yes	Yes	[a]	[a]	No

[a] May be required, depending on the nature of the specific test.

CATEGORY I

Analytical procedures for quantitation of major components of bulk drug substances or active ingredients (including preservatives) in finished pharmaceutical products.

CATEGORY II

Analytical procedures for determination of impurities in bulk drug substances or degradation compounds in finished pharmaceutical products. These procedures include quantitative assays and limit tests.

CATEGORY III

Analytical procedures for determination of performance characteristics (e.g., dissolution, drug release, and others).

CATEGORY IV

Identification tests.

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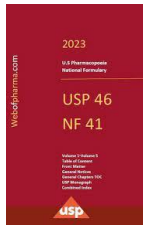
USP <1226> Verification of compendial procedures



(USP <1226> abstract)

VERIFICATION REQUIREMENTS

Verification requirements should be based on an assessment of the complexity of both the procedure and the material to which the procedure is applied.

Complexity to consider for the assessment:

- level of training and experience of the user
- type of procedure
- associated equipment or instrumentation
- which product is being tested.

Verification is not required for basic compendial test procedures, as **loss on drying, residue on ignition,** various **wet chemical procedures** such as acid value, and simple instrumental determinations such as **pH measurements**.

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EP Chapter 5.26 implementation of Pharmacopoeial procedures and comparison with USP

What we have seen

- Analytical methods & Compendial monograph
- Verification vs Validation
- EP Chapter 5.26 Implementation of Pharmacopoeial Procedures
- USP <1226> Verification of Compendial Procedure

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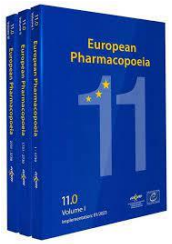
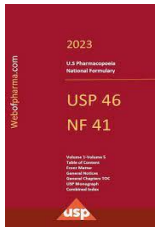
EP Chapter 5.26 implementation of Pharmacopoeial procedures and comparison with USP – CONCLUSION

EP Chapter 5.26 (Implementation of Pharmacopoeial Procedures) gives **similar indication** as USP <1226> (Verification of Compendial Procedures) about the requirements of the implementation and verification of the compendial procedures.





- **Similarities**: compendial methods do not need a full validation, definitions of verification and validation, assessment for considering the verification parameters to evaluate.
- **Differences**: EP defines which parameters should be considered in evaluation, USP refers to the validation parameters table.

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Thanks!

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