Validation and Verification of Compendial Methods

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Outline

- Background and Requirements
- Impact of the USP Stimulus article
- Method Characteristics
- What should be included in a Method Verification protocol
Please Define...

- Validation
- Test Method Validation
- VALIDATION
- Qualification
- Verification
- Compendial Method
Please Define...

- USP Monograph
- USP Chapter
- USP Stimulus article
- Intended use
- Suitable
- Analytical Target Profile
Qualification vs. Validation

➢ Qualification
  ❖ Documented Evidence Suitable for Intended Use
  ❖ Report on Development of Method and Evaluation of Method
  ❖ Important Validation Parameters

➢ Validation
  ❖ Pre Determined Acceptance Criteria for Appropriate
  ❖ Pre-Validation Characteristics for Test Category
  ❖ Prospective Study – Criteria Based on Data from
  ❖ Qualification of Method/Pre-Validation Studies
Verification

- Synonym
  - Confirmation
  - Corroboration
  - Proof
  - Substantiation
  - Authentication
  - Certification

- Antonym
  - Contradiction
Suitability

- Synonym
  - Appropriateness
  - Aptness
  - Fittingness
  - Fitness
  - Correctness

- Antonym
  - Unsuitability
Validation of an analytical method

The process by which it is established, by laboratory studies, that the performance characteristics of the method meet the requirements for the intended analytical applications.
Users of compendial procedures are not required to validate these procedures when first used in their laboratories, but documented evidence of suitability should be established under actual conditions of use.
Verification of an analytical method

The process by which it is established, by laboratory studies, that the performance characteristics of a compendial method meet the requirements for the intended use in the intended location.
Although complete revalidation of a compendial method is not required to verify the suitability of the method under actual conditions of use, some of the analytical performance characteristics listed in chapter <1225> Table 2 may be used for the verification process
Only those characteristics that are considered to be appropriate for the verification of the particular method need to be validated. The degree and extent of the verification process may depend on the level of training and experience of the user, on the type of procedure and its associated equipment or instrumentation, on the specific procedural steps, and on which article(s) are being tested.
Warning Letter

The test methods performed for **** USP have not been verified to ensure suitability under actual conditions of use

WL-320-08-01
Warning Letter

Our inspection found that you have not ensured that certain USP compendial test methods were verified under actual conditions of use. Specifically, you have failed to conduct adequate verification of USP compendial test methods as applied to the production of your firm's API. The data you provided in your ****, response did not include information about the suitability, accuracy, and detection limits of certain test methods for API, such as the protein test method, used by your firm.

WL-320-08-01
Warning Letter

There was no indication from these data that your firm's test methods could reliably detect and quantify the presence of proteins in the finished API. In addition, your firm had not conducted suitability testing of the method to determine the limit of detection for the method. The suitability for use of the protein method for in-process testing was also not established.
In your response to the FDA-483, you state that the firm has conducted suitability tests. In addition, you state that the test method was not verified because it was a basic compendial test.
Warning Letter

You assert that USP <1226>, Verification of Compendial Procedures, states that verification is not required for basic compendial test procedures that are routinely performed unless there is an indication that the compendial procedure is not appropriate for the article under test. In your response, you also state that the laboratory performed basic suitability testing on the *** API analytical method in accordance with your standard operating procedures (SOPS).
Warning Letter

We disagree with your assertions that verification is not required for those USP test methods used by your firm. In accordance with cGMP, analytical methods should be validated unless the methods used are included in a relevant pharmacopoeia or other recognized standard reference. If the method is a compendial method, verification of the methods should be conducted to determine that the method is suitable for its intended use under actual conditions.

WL-320-08-01
Warning Letter

We acknowledge that the USP informational chapter <1226> suggests that there is a lesser need for verification for the simplest tests such as loss on drying, residue on ignition, and pH measurements. However, these do not include the test methods at issue, including the **** test method.
USP Monograph
USP Chapter
USP <1224>
USP <1225>
USP <1226>
When were they written
The impact of recent guidances
ICH Q10

Pharmaceutical Quality System
ICH Q10 Pharmaceutical Quality System

Pharmaceutical Development
Technology Transfer
Commercial Manufacturing
Product Discontinuance

Investigational Products

GMP

Management Responsibilities

Process Performance and Product Quality Monitoring System
Corrective Action/Preventive Action (CAPA) System
Change Management System
Management Review

PQS Elements

Knowledge Management

Quality Risk Management

Enablers

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# Product Lifecycle

<table>
<thead>
<tr>
<th>Pharmaceutical Development</th>
<th>Technology Transfer</th>
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Guidance for Industry

Process Validation: General Principles and Practices

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Veterinary Medicine (CVM)

January 2011
Current Good Manufacturing Practices (CGMP)
Revision 1
Process Validation

The collection and evaluation of data from process design stage through commercial production, which established scientific evidence that the process is capable of consistently delivering quality product.

It involves a series of activities taking place over the lifecycle of the process.
Stage 1 – Process Design: The commercial process is defined during this stage based on knowledge gained through development and scale-up activities.

Stage 2 – Process Qualification: During this stage, the process design is confirmed as being capable of reproducible commercial manufacturing.

Stage 3 – Continued Process Verification: Ongoing assurance is gained during routine production that the process remains in a state of control.
A test method is a process.
Test Method Validation

The collection and evaluation of data, from the method design and development, throughout material testing, which establishes scientific evidence that the method is capable of consistently delivering results that accurately reflect the material quality attribute.

involves a series of activities taking place over the lifecycle of the method.
Stage 1 – **Method Design**: The quality control test is defined during this stage based on knowledge gained through material discovery and product and method development.

Stage 2 – **Method Transfer**: During this stage, the method design is confirmed as being capable of reproducible performance in the quality control laboratory.

Stage 3 – **Continued Method Performance Verification**: Ongoing assurance is gained during routine testing that the test method remains in a state of control.
A Rejuvenated Player

The

USP
USP Validation and Verification
Expert Panel


Pharmaceutical Forum 39(6)
It will replace:

- <1224> Transfer of Analytical Procedures
- <1225> Validation of Compendial Procedures
- <1226> Verification of Compendial Procedures

USP Stimulus
ICH [Q2(R1)] and USP [<1225>] provide guidance pertaining to procedure suitability as part of the procedure validation exercise (accuracy, precision, specificity, etc.), but they do not provide a framework that allows users to reliably understand and control sources of variability.
Enhanced understanding of variables that affect the performance of the analytical procedure provides greater assurance of the quality attributes of the tested product can be reliably assessed.

Understand the variability

USP Stimulus
Method Development and Design

Process Performance Qualification

Process Performance Verification
# Product/Test Method Lifecycle

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**Knowledge**

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The Lifecycle approach to TMV

➢ Will require a cultural change.
➢ Will require the application of The Pharmaceutical Quality System throughout all of the organization, through the complete product and test method lifecycle.
➢ Expects communication throughout the organization.
Compendial Test Method Verification
Users of compendial procedures are not required to validate these procedures when first used in their laboratories, but documented evidence of suitability should be established under actual conditions of use.
Verification of an analytical method

The process by which it is established that a compendial method is suitable for the intended use in the intended environment.
Suitable

For its intended use
Effective

• Method Development
• Method validation
• Method verification

Is dependent upon

• a clear set of requirements
• A complete understanding of the intended use
Intended use

Target Analytical Profile

Acceptance Criteria
Analytical Target Profile

A fundamental component of the lifecycle approach to analytical procedures is having a predefined objective that stipulates the performance requirements for the analytical procedure. These requirements are derived from the Analytical Target Profile (ATP).
The Analytical Target Profile

Well identify

- Method type
- Method characteristics
Analytical Target Profile - Assay

The procedure must be able to quantify [an analyte] in the presence of [X, Y, Z] over a range of A% to B% of the nominal concentration with an accuracy and uncertainty so that the reportable result falls within ± C% of the true value with at least 90% probability determined with 95% confidence.
The procedure must be able to quantify [an impurity] in the presence of components that are likely to be present in the sample within the range from the reporting threshold to the specification limit. The accuracy and precision of the procedure must be such that the reportable result falls within $\pm D\%$ of the true value for impurity levels of 0.05% to 0.15% with 80% probability with 95% confidence, and within $\pm E\%$ of the true value for impurity values $>0.15\%$ with 95% probability determined with 95% confidence.
Is there more to be considered in method verification?
Verification of an analytical method

The process by which it is established that a compendial method is suitable for the intended use in the intended environment.
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