Development of a New USP General Information Chapter:
Verification of Compendial Procedures

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The purpose of USP's proposed General Chapter (1226) "Verification of Compendial Procedures" is to provide guidance about the verification process.

Calibration, validation, and traceability are central components of metrology (1–3). The process of validating a new analytical procedure for compendial usage is addressed in US Pharmacopeia (USP) General Chapter (1225) "Validation of Compendial Procedures" (4).

Even though a USP procedure is fully validated, one may not have assurance that the procedure is suitable for use with a specific ingredient or product, in a specific laboratory, with specific laboratory personnel, equipment, and reagents. The latter falls within the area termed verification, whereby analysts demonstrate that a validated procedure to be used for the first time with a particular product will yield acceptable results using a given laboratory’s equipment, personnel, and reagents. Therefore, the purpose of the proposed General Chapter (1226) "Verification of Compendial Procedures" (5) is to provide guidance about the verification process.

USP developed this chapter in response to industry’s requests to provide instructions for verifying compendial procedures. The authors note that verification is not mandatory unless an enforcing body adopts it by reference, it is referenced in a specific USP monograph, or it is adopted by a specific manufacturer in standard operating procedures subject to current good manufacturing practices (CGMPs) regulations (see also General Chapters, USP General Notices).

A compendial procedure is considered validated if it is published as official text in USP—National Formulary (NF), in a supplement, or as an Interim Revision Announcement in Pharmacopeial Forum (PF). Therefore, users of such procedures are not required to perform validation studies. But, they must demonstrate that the use of the official procedure is suitable given the actual conditions of use. This requirement is established by the US Food and Drug Administration’s CGMPs, which state “The suitability of all testing methods used shall be verified under actual conditions of use” (6).

The suitability of a compendial procedure may be an issue for an article under test for several reasons (e.g., different impurity profiles from different routes of synthesis, composition of formulations, or interference from excipients). General Chapters already exist in the USP on the general topic. For example, various General Chapters for microbiological testing describe approaches that will ensure the article to be tested is suitable for use with the validated procedure. Similarly, many USP monographs have sections devoted to establishing the suitability of chromatographic systems.

If multiple laboratories are expected to use the compendial procedure with essentially the same conditions of actual usage, then one laboratory may perform the verification. With appropriate verification of adequate robustness, other locations may use the verified procedure. Some factors that must be considered when ascertaining usage conditions are:

- article to be tested;
- laboratories to be used;
- equipment to be used;
- personnel;
- reagents.

**Verification process**

It is assumed that personnel involved in the verification process possess appropriate experience, knowledge, and training to execute a verification properly. A critical step in the verification process is the preparation of a document describing:

- procedures to be verified;
- number and identity of lots or batches of articles that will be used (note that the verification may need to be repeated for different types of articles);
- analytical performance characteristics to be evaluated.

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*The proposal to replace "Methods" in the title with "Procedures" was made in Pharmacopeial Forum 31 (2) and will become official in USP 29 (Suppl. 1).*
evaluated, along with a specification of the acceptable range of results expressed in terms of acceptable accuracy, precision, or linearity parameters;

- justification of any deviations from the recommendations in General Chapter (1226).

A critical part of the process is to pre-establish acceptance criteria for the verification attributes being tested. These criteria vary with the intended use of the procedure. Upon completion of sample analysis, laboratory personnel should compare the data obtained with the pre-established acceptance criteria. The ensuing documentation should include a summary of analytical data, a comparison of the data with acceptance criteria, and a conclusion about the suitability of the validated procedure under actual usage conditions. If the data meet the acceptance criteria, it may be assumed that the compendial procedure will perform as intended under actual usage conditions.

If the analytical data do not compare favorably with the pre-established acceptance criteria, one should try to determine the sources of the deviations and initiate corrective action (when appropriate), which may include rectifying training deficiencies or contacting USP personnel for clarification of the procedure. Any corrective actions should

### Table I: Data elements for verification of dosage substances and excipients

<table>
<thead>
<tr>
<th>Technique</th>
<th>Category I</th>
<th>Category II</th>
<th>Category III</th>
<th>Category IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPLC–GC</td>
<td>Precision</td>
<td>Precision, specificity, quantitation, limit</td>
<td>Specificity, detection, limit</td>
<td>N/A</td>
</tr>
<tr>
<td>Spectrophotometric/ colorimetric</td>
<td>Precision</td>
<td>Precision, quantitation, limit</td>
<td>Specificity, detection, limit</td>
<td>N/A</td>
</tr>
<tr>
<td>Titrimetric</td>
<td>Precision</td>
<td>Precision</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>TLC</td>
<td>N/A</td>
<td>Specificity, quantitation, limit</td>
<td>Specificity, detection, limit</td>
<td>N/A</td>
</tr>
<tr>
<td>Gas electrophoresis</td>
<td>N/A</td>
<td>Specificity, quantitation, limit</td>
<td>Specificity, detection, limit</td>
<td>N/A</td>
</tr>
</tbody>
</table>

*Reproduced with permission from the US Pharmacopeia. Abbreviations: HPLC–GC is high-performance liquid chromatography–gas chromatography. N/A is not applicable. TLC is thin-layer chromatography.
be indicated in a revised verification approval document. The final document and its components should contain the initial unacceptable results.

Despite repeated attempts to perform the procedure and obtain acceptable results, the results may demonstrate that the procedure is not suitable for application under specific usage conditions. In such a case, it may be necessary to modify the official compendial procedure (in which case, suggestions for improvement should be submitted to USP), develop and validate an alternative procedure, change the matrix to overcome potential interferences, or make other changes.

If an alternative procedure is validated, the new procedure and supporting validation data can be submitted to USP for consideration as part of a flexible monograph. Flexible monographs allow alternative tests, procedures, and acceptance criteria to account for control of quality attributes that may differ between articles of the same compendial name. If a compendial procedure is deemed unsuitable after consultation with USP scientists, then the final verification document should summarize the steps to demonstrate suitability of the new procedure and to describe the final action taken in developing the alternative procedure.

The characteristics chosen for use in the verification process typically are derived from those used in validation studies. Table II in General Chapter (1225) provides a listing of the performance characteristics that should be assessed based in different analytical categories. *Category I* encompasses procedures intended to quantify major components of drug substances in finished dosage forms. *Category II* covers procedures intended for use as either quantitative or limit testing for impurities. *Category III* refers to procedures such as dissolution intended to assess dosage-form performance. *Category IV* includes identification procedures. All the characteristics in Table II are not required for procedure verification.

Table I in proposed General Chapter (1226) lists the data elements that should be evaluated for procedure verification for drug substances and excipients (see Table I).

Table II in proposed General Chapter (1226) lists the data elements that should be evaluated for procedure verification for dosage forms (see Table II). The number of tests for the verification of procedures for use with drug products is larger for several categories because of the increased complexity of drug products, in comparison with drug substances and excipients. Additional performance characteristics may be appropriate for verification purposes. For example, if a pharmaceutical manufacturer wants to make deliberate modifications in a procedure in terms of analyst, equipment, reagent, or environmental condition, then robustness studies are appropriate. Definitions for robustness are listed in General Chapter (1225). In particular cases, the stability of the sample preparation should be investigated because different matrices can affect the stability of the solution.
Inside USP

Status of the new chapter
After General Chapter (1226) was published in PF, USP received numerous comments from pharmaceutical manufacturers and regulators. As specified in the briefing, the deadline was July 15, 2005. USP deferred this deadline in anticipation of discussions at the USP Annual Scientific Meeting in September 2005. A summary of the comments and USP responses follows.

Some respondents indicated that by including elements of validation in the verification process, USP is calling into question one key principle (and advantage) of a compendial procedure: it is robust and validated. It should be understood that the proposed chapter is not focused on challenging the validity of the procedure per se, but rather the suitability of the analytic system (i.e., a matrix of factors such as the article to be tested, the laboratories to be used, the equipment to be used, the personnel involved, and reagents used, etc.).

Other respondents suggested that the range of results that will be considered acceptable represents knowledge typically available only to the group that performed the original validation. Thus, a laboratory testing a compendial article for the first time will have no way of knowing in advance what results would be acceptable—other than those defined by the specification range. USP believes that acceptance criteria verification...
should be selected according to a risk-based approach according to the intended use of the procedure and justified in the verification protocol.

Another respondent stated concern related to the issue of “grandfathering” because numerous official procedures have been in place for years and have been used without being subjected to formal verification procedures. Some respondents asked that a provision be added indicating that the intent of the proposed chapter is to provide guidance for verifying the suitability of newly adopted procedures and not for retroactive application to those being performed successfully. USP agrees with this concern and will provide public statement to support its prospective use.

Some respondents suggested that an organization performing a verification exercise should have the freedom to document its process in a defensible manner. These pharmaceutical manufacturers were concerned that words like “typically” and “may” sometimes are reinterpreted, particularly in regulatory contexts, as “must.” Further, these respondents suggested that submission of information associated with the resolution of verification issues should be at the discretion of the pharmaceutical manufacturer that was performing the verification activities. As a variation on these observations, some respondents noted that contract laboratories perform numerous procedures for different materials submitted by client companies. In an outsourcing context, it may be very difficult to verify the suitability of the compendial procedure for a large number of articles. USP generally supports these observations and notes (as stated above) that the proposed chapter does not specify a requirement except under the circumstances noted. Manufacturers may use all, none, or part of the proposed chapter, when finalized, at their discretion.

Finally, some respondents suggested that it is inappropriate to combine drug substances and excipients in the same table because the types and requirements of procedures for these two very different articles can vary broadly. USP notes this point and will attempt to clarify the distinction as the proposed chapter moves to finalization.

**Conclusion**

Procedures published as official text in the USP-NF are considered validated. Therefore, the user of an official procedure does not have to perform a full validation study. But, CGMPs require the demonstration that a compendial procedure can be used successfully for a given article, a process known as verification. USP’s proposed new general information chapter (1226) “Verification of Compendial Procedures” is intended to fill the gap in the proper usage of compendial procedures by outlining a process for verifying their suitability.

A new version of (1226) is scheduled to appear in the May–June issue of PF. USP is amenable to the receipt of comments about chapters and monographs that are in development or are official. USP encourages industry and others to review the chapter and submit comments. Finalization of the proposed chapter is the General Chapters Expert Committee’s responsibility.

**References**

1. W. May et al., Definitions of Terms and Modes Used at NIST for Value-Assignment of Reference Materials for Chemical Measurements (National Institute of Standards and Technology [NIST], Gaithersburg, MD, Jan. 2000).
6. 21 CFR 211.194(a)(2).