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⟨1467⟩ RESIDUAL SOLVENTS—VERIFICATION OF COMPENDIAL PROCEDURES AND VALIDATION OF ALTERNATIVE PROCEDURES

The procedures defined in *Residual Solvents* ⟨467⟩ have been validated for Class 1 and 2 solvents over the range of 50%–150% of the concentrations described in the standard preparation for procedures A and B in *Residual Solvents* ⟨467⟩, *8. Analytical Procedures for Class 1 and Class 2 Residual Solvents*.

The suitability of these residual solvent procedures must be verified under actual conditions of use. When using the procedures for testing residual solvents described in ⟨467⟩, verification can be accomplished using the recommendations below. There are separate recommendations for limit and quantitative procedures in *Residual Solvents* ⟨467⟩, *8. Analytical Procedures for Class 1 and Class 2 Residual Solvents*.

Alternative procedures include different analytical procedures from those described in ⟨467⟩, as well as modifications to the procedures described therein that go beyond the stated validation of the method (e.g., different concentrations or other analytes or variations to chromatographic conditions beyond those permitted by *Chromatography* ⟨621⟩). Alternative procedures are permitted (see *General Notices, 6.30 Alternative and Harmonized Methods and Procedures*), provided that they are properly validated. A risk-based approach may be appropriate to determine the degree and extent of the verification or validation process to assure the fitness for purpose of the procedure. Recommendations for validation of alternative procedures (limit and quantitative tests) are described in *Validation of Alternative Procedures*. A summary of the requirements is shown in *Table 1*.

Table 1. Summary of Verification and Validation Requirements

	Verification of Compendial Procedures		Validation of Alternative Procedures	
Validation/Verification Characteristics	**Limit Test Methods**	**Quantitative Methods**	**Limit Test Methods**	**Quantitative Methods**
Specificity	Yes	Yes	Yes	Yes
Detection limit	Yes[a]	No	Yes	No
Quantitation limit[b]	No	Yes[a]	No	Yes
Accuracy	No	Yes	No	Yes
Precision/repeatability	No	Yes	No	Yes
Linearity	No	No	No	Yes
Range	No	Demonstrated by accuracy and precision	No	Demonstrated by accuracy and precision
Intermediate precision	No	No	No	Yes
Solution stability[c]	Yes	Yes	Yes	Yes
Robustness[d]	No	No	Yes[e]	Yes[e]

[a] System suitability may be used instead to demonstrate sensitivity.

[b] In quantitative tests, quantitation limit may be demonstrated by accuracy and precision determination.

[c] Solution stability should be determined for the timeline of the test.

[d] Evaluation of robustness should be considered during the development phase and depends on the type of procedure under study.

[e] The "Yes" quotation here is intended to emphasize the importance of assessing the robustness of the procedure before the implementation.

Change to read:

VERIFICATION OF COMPENDIAL PROCEDURES

Limit Procedures: Procedure A and Procedure B

The analytical characteristics to be verified include specificity, detectability, and solution stability.

VERIFICATION WHEN SOLVENTS LIKELY TO BE PRESENT (LTBP) ARE NOT KNOWN

Samples

Prepare a reagent blank.

Prepare *Standard solutions* as described in *Residual Solvents* ⟨467⟩, *8. Analytical Procedures for Class 1 and Class 2 Residual Solvents, 8.2 Screening of Water-Soluble Articles* or *8.3 Screening of Water-Insoluble Articles*.

Prepare the *Spiked sample solution* as described in *Class 1 System suitability solution* in *Residual Solvents* ⟨467⟩, *8. Analytical Procedures for Class 1 and Class 2 Residual Solvents, 8.2 Screening of Water-Soluble Articles* or *8.3 Screening of Water-Insoluble Articles*.

Specificity

Recommended acceptance criteria: An appropriate blank should be injected to assure the lack of a significant interference. A significant interference is one producing a deviation in the fitness for purpose of the procedure that affects precision and/or accuracy. The procedure must be able to separate acetonitrile and methylene chloride (*Procedure A* in *Residual Solvents* ⟨467⟩, *8. Analytical Procedures for Class 1 and Class 2 Residual Solvents, 8.2 Screening of Water-Soluble Articles* or *8.3 Screening of Water-Insoluble Articles*), or ▲methylisobutylketone▲ (ERR 1-Dec-2020) and *cis*-dichloroethene (*Procedure B* in *8. Analytical Procedures for Class 1 and Class 2 Residual Solvents, 8.2 Screening of Water-Soluble Articles* or *8.3 Screening of Water-Insoluble Articles*) with a resolution of NLT 1.0.

Detection Limit (see Table 1, Footnote a)

Recommended acceptance criteria: The mean signal-to-noise ratio for each solvent in the *Standard solution* and *Spiked sample solution* [after correction for native (original) solvent content] from at least three determinations from a single preparation is NLT 3.

Solution Stability

Recommended acceptance criteria: Detection limit should meet the requirements throughout the testing period.

VERIFICATION WHEN SOLVENTS LTBP ARE KNOWN

Samples

Prepare a reagent blank.

Prepare *Standard solution(s)* and *Sample solution(s)* as described in *Residual Solvents* ⟨467⟩, *8. Analytical Procedures for Class 1 and Class 2 Residual Solvents, 8.2 Screening of Water-Soluble Articles* or *8.3 Screening of Water-Insoluble Articles* depending on the specific sample solubility using only those solvents likely to be present (LTBP).

Prepare *Spiked sample solution(s)* as described in *Quantitative Procedures: Procedure C* for solvents LTBP [corrected for native (original) solvent content].

Specificity

Recommended acceptance criteria: The reagent blank does not produce any significant interference with any of the peaks from solvents LTBP.

The procedure must be able to separate each of the solvents in the *Standard solution(s)* from each other and from other peaks in the *Spiked sample solution* with a resolution of NLT 1.0. If the resolution between any pair of peaks is less than 1.5, then verification must demonstrate that the method is suitable for its intended use.

If the solvents present in the *Standard solution(s)* are not separated with a resolution of NLT 1.0 when using the *Chromatographic System* of *Procedure A*, then *Procedure B* in *Residual Solvents* ⟨467⟩, *8. Analytical Procedures for Class 1 and Class 2 Residual Solvents, 8.2 Screening of Water-Soluble Articles* or *8.3 Screening of Water-Insoluble Articles* should be used as confirmatory.

Detection Limit

Recommended acceptance criteria: The mean signal-to-noise ratio for each solvent in the *Standard solution* and the *Spiked sample solution* [after correction for native (original) solvent content] from at least three determinations from a single preparation is NLT 3.

Solution Stability

Recommended acceptance criteria (not required if only running fresh solutions): Detection limit for limit tests and quantitation limit for quantitative tests should be met throughout the testing period.

Quantitative Procedures: Procedure C

[Note—When performing *Residual Solvents* ⟨467⟩, *8. Analytical Procedures for Class 1 and Class 2 Residual Solvents, 8.5 Quantitative Tests—Procedure C*, solvents LTBP are typically known, either based on results from *Procedure A* or *Procedure B* in *Residual Solvents* ⟨467⟩, *8. Analytical Procedures for Class 1 and Class 2 Residual Solvents, 8.2 Screening of Water-Soluble Articles* or *8.3 Screening of Water-Insoluble Articles*, or based on available knowledge. The analytical characteristics to be verified include specificity, accuracy (which addresses quantitation limit), range, repeatability, and solution stability.]

Samples

Prepare a reagent blank.

Standard stock solution: Prepare a solution containing each solvent LTBP or each peak identified and verified by *Procedure A* and *Procedure B* in *Residual Solvents* ⟨467⟩, *8. Analytical Procedures for Class 1 and Class 2 Residual Solvents, 8.2 Screening of Water-Soluble Articles* or *8.3 Screening of Water-Insoluble Articles*, with a concentration as described in *Residual Solvents* ⟨467⟩, *8. Analytical Procedures for Class 1 and Class 2 Residual Solvents, 8.5 Quantitative Tests—Procedure C* for water-soluble articles or water-insoluble articles, as appropriate.

Sample stock solution: Prepare as described in *Residual Solvents* ⟨467⟩, *8. Analytical Procedures for Class 1 and Class 2 Residual Solvents, 8.2 Screening of Water-Soluble Articles* or *8.3 Screening of Water-Insoluble Articles*.

Spiked sample solution: Prepare as described in *Residual Solvents* ⟨467⟩, *8. Analytical Procedures for Class 1 and Class 2 Residual Solvents, 8.5 Quantitative Tests—Procedure C*, using the *Standard stock solution*.

Spiked sample solutions A, B, C, etc.: Prepare *Spiked sample solutions* with the sample matrix and spiked with each solvent LTBP or identified and verified by *Procedure A* and *Procedure B* in *Residual Solvents* ⟨467⟩, *8. Analytical Procedures for Class 1 and Class 2 Residual Solvents, 8.2 Screening of Water-Soluble Articles* or *8.3 Screening of Water-Insoluble Articles*, in triplicate, at NLT 3 levels covering the range of interest or at least 50%–150% of the corresponding concentration of the *Standard solution* as described in *Procedure A* in *8. Analytical Procedures for Class 1 and Class 2 Residual Solvents, 8.2 Screening of Water-Soluble Articles* or *8.3 Screening of Water-Insoluble Articles*. [Note—The *Spiked sample solution* may be used as one of the solutions.]

Specificity

Recommended acceptance criteria: The procedure must be able to separate each of the solvents in the *Standard solution(s)* from each other and from other peaks in the *Spiked sample solution* with a resolution of NLT 1.0. If the resolution between any pair of peaks is less than 1.5, then verification must demonstrate that the method is suitable for its intended use.

If the solvents present in the *Standard solution(s)* are not separated with a resolution of NLT 1.0, then chromatography described in *Procedure B* in *Residual Solvents* ⟨467⟩, *8. Analytical Procedures for Class 1 and Class 2 Residual Solvents, 8.2 Screening of Water-Soluble Articles* or *8.3 Screening of Water-Insoluble Articles* should be used as confirmatory.

Quantitation Limit

Recommended acceptance criteria: The mean signal-to-noise ratio for each solvent in the *Standard solution* and the *Spiked sample solution* [after correction for native (original) solvent content] from at least three determinations is NLT 10, or the *Quantitation Limit* may be demonstrated by *Accuracy* and *Precision*.

Accuracy

Recommended acceptance criteria: The mean recovery for *Spiked sample solutions A*, *B*, and *C, etc.*, when calculated relative to the *Spiked sample solution*, is 80%–120% of the expected theoretical amount.

[Note—Recoveries should be corrected for native (original) content of any solvent under test.]

Precision/Repeatability

Use at least six independent *Spiked sample solution* preparations from the same lot, prepared as described in the *Spiked sample solution* in the *Accuracy* test above, or use nine independent preparations as described in *Spiked sample solutions A*, *B*, *C, etc*.

Recommended acceptance criteria: Relative standard deviation is NMT 20% for each solvent present.

Solution Stability: Demonstrate acceptable solution stability for the period of time to run the test.

Recommended acceptance criteria: NMT 20% change in solvent(s) content compared to the initial time point

VALIDATION OF ALTERNATIVE PROCEDURES

Chromatographic alternative procedures should meet the acceptance criteria for the analytical performance characteristics shown below. When non-chromatographic alternative procedures are validated, the analytical performance characteristics listed should be addressed, although, it may be appropriate to apply other analytical performance characteristics. For more information, refer to *Validation of Compendial Procedures* ⟨1225⟩.

Limit Procedures

Analytical characteristics to be validated are specificity, detection limit, and solution stability. The same criteria used for *Verification when solvents LTBP are known*, as described above, may be used.

Quantitative Procedures

Analytical characteristics to be validated are specificity, linearity and range, quantitation limit, accuracy, repeatability, intermediate precision, and solution stability.

Samples

Prepare a reagent blank.

Spiked sample solutions P, Q, R, etc.:

Prepare *Spiked sample solutions* with the sample matrix and spiked with each solvent LTBP at NLT 5 levels covering the range of interest. [Note—Results should be corrected for native (original) content of any solvent under test.]

Specificity

Recommended acceptance criteria: The analytical procedure must have the ability to assess unequivocally the analytes of interest in the presence of the components expected to be present.

Linearity and Range

Recommended acceptance criteria: Perform linear regression analysis on the results for *Spiked sample solutions P, Q, R, etc*. The coefficient of determination, r^2, is NLT 0.90.

Quantitation Limit

Recommended acceptance criteria: The mean signal-to-noise ratio for each solvent in the standard solution and the *Spiked sample solution* [after correction for native (original) solvent content] from at least three determinations is NLT 10. The *Quantitation Limit* may also be demonstrated by *Accuracy* and *Precision*.

Accuracy

Recommended acceptance criteria: The mean recovery for each *Spiked sample solution* should be 80%–120%.

[Note—Recoveries should be corrected for native (original) content of any solvent under test.]

Precision/Repeatability:

Prepare at least six independent *Spiked sample solution* preparations from the same lot.

Recommended acceptance criteria: Relative standard deviation is NMT 20% for each solvent present.

Precision/Intermediate Precision:

Perform the *Repeatability* test over at least two independent events, e.g., on different days, and/or using different instruments and/or analysts.

Recommended acceptance criteria: Testing for intermediate precision should demonstrate that the method is suitable for its intended use.

Solution Stability:

Standard solutions and *Spiked sample solutions* should be stable throughout the testing period.

Recommended acceptance criteria: NMT 20% variation

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
<1467> RESIDUAL SOLVENTS- VERIFICATION OF COMPENDIAL PROCEDURES AND VALIDATION OF ALTERNATIVE PROCEDURES	Edmond Biba Senior Scientific Liaison	GCCA2020 General Chapters - Chemical Analysis 2020

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