

{467} RESIDUAL SOLVENTS

(Chapter under this new title—to become official July 1, 2007)
(Current chapter title is {467} Organic Volatile Impurities)

Change to read:

IDENTIFICATION, CONTROL, AND QUANTIFICATION OF RESIDUAL SOLVENTS

•Whenever possible, the substance under test needs to be dissolved to release the residual solvent. Because the USP deals with drug products, as well as active ingredients and excipients, it may be acceptable that in cases some of the components of the formulation will not dissolve completely. In those cases, the drug product may first need to be pulverized into a fine powder so that any residual solvent that may be present can be released. This operation should be as fast as possible to prevent the loss of volatile solvents during the procedure.●₃

NOTE—The organic-free water specified in the following procedures produces no significantly interfering peaks when chromatographed.

Class 1 and Class 2 Residual Solvents

•The following procedures are useful to identify and quantify residual solvents when the information regarding which solvents are likely to be present in the material is not available. When the information about the presence of specific residual solvents is available, only *Procedure C* is needed to quantify the amount of residual solvents present.●₃

WATER-SOLUBLE ARTICLES

Procedure A—

Class 1 Standard Stock Solution—Transfer 1.0 mL of USP Class 1 Residual Solvents Mixture RS to a 100-mL volumetric flask, add 9 mL of dimethyl sulfoxide, dilute with water to volume, and mix. Transfer 1.0 mL of this solution to a 100-mL volumetric flask, dilute with water to volume, and mix. Transfer 1.0 mL of this solution to a 10-mL volumetric flask, dilute with water to volume, and mix.

Class 1 Standard Solution—Transfer 1.0 mL of *Class 1 Standard Stock Solution* to an appropriate headspace vial, add 5.0 mL of water, apply the stopper, cap, and mix.

Class 2 Standard Stock Solutions—Transfer 1.0 mL of USP Residual Solvents Class 2—Mixture A RS to a 100-mL volumetric flask, dilute with water to volume, and mix. This is *Class 2 Standard Stock Solution A*. Transfer 1.0 mL of USP Residual Solvents Class 2—Mixture B RS to a 100-mL volumetric flask, dilute with water to volume, and mix. This is *Class 2 Standard Stock Solution B*.

Class 2 Mixture A Standard Solution—Transfer 1.0 mL of *Class 2 Standard Stock Solution A* to an appropriate headspace vial, add 5.0 mL of water, apply the stopper, cap, and mix.

Class 2 Mixture B Standard Solution—Transfer 5.0 mL of *Class 2 Standard Stock Solution B* to an appropriate headspace vial, add 1.0 mL of water, apply the stopper, cap, and mix.

Test Stock Solution—Transfer about 250 mg of the article under test, accurately weighed, to a 25-mL volumetric flask, dissolve in and dilute with water to volume, and mix.

Test Solution—Transfer 5.0 mL of *Test Stock Solution* to an appropriate headspace vial, add 1.0 mL of water, apply the stopper, cap, and mix.

Class 1 System Suitability Solution—Transfer 1.0 mL of *Class 1 Standard Stock Solution* to an appropriate headspace vial, add 5.0 mL of *Test Stock Solution*, apply the stopper, cap, and mix.

Chromatographic System (see *Chromatography* (621))—The gas chromatograph is equipped with a flame-ionization detector, a 0.32-mm × 30-m fused-silica column coated with a 1.8-μm layer of phase G43 or a 0.53-mm × 30-m wide-bore column coated with a 3.0-μm layer of phase G43. The carrier gas is nitrogen or helium with a linear velocity of about 35 cm per second, and a split ratio of 1 : 5. ●[NOTE—Split ratio can be modified in order to optimize sensitivity.]●₃ The column temperature is maintained at 40° for 20 minutes, then raised at a rate of 10° per minute to 240°, and maintained at 240° for 20 minutes. The injection port and detector temperatures are maintained at 140° and 250°, respectively. Chromatograph the *Class 1 Standard Solution*, *Class 1 System Suitability Solution*, and *Class 2 Mixture A Standard Solution*, and record the peak responses as directed for *Procedure*: the signal-to-noise ratio of 1,1,1-trichloroethane in the *Class 1 Standard Solution* is not less than 5; the signal-to-noise ratio of each peak in the *Class 1 System Suitability Solution* is not less than 3; and the resolution, *R*, between acetonitrile and methylene chloride in the *Class 2 Mixture A Standard Solution* is not less than 1.0.

Procedure—Separately inject (following one of the headspace operating parameter sets described in the table below) equal volumes of headspace (about 1.0 mL) of the *Class 1 Standard Solution*, *Class 2 Mixture A Standard Solution*, *Class 2 Mixture B Standard Solution*, and the *Test Solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. ●If a peak response of any peak, other than a peak for 1,1,1-trichloroethane, in the *Test Solution* is greater than or equal to a corresponding peak in either the *Class 1 Standard Solution* or either of the two *Class 2 Mixture Standard Solutions*, or a peak response of 1,1,1-trichloroethane is greater than or equal to 150 times the peak response corresponding to 1,1,1-trichloroethane in the *Class 1 Standard Solution*, proceed to *Procedure B* to verify the identity of the peak; otherwise the article meets the requirements of this test.●₃

Table 5. Headspace Operating Parameters

	Headspace Operating Parameter Sets		
	1	2	3
Equilibration temperature (°)	80	105	80
Equilibration time (min.)	60	45	45
Transfer-line temperature (°)	85	110	105
Carrier gas: nitrogen or helium at an appropriate pressure			
Pressurization time (s)	30	30	30
Injection volume (mL)	1	1	1

Procedure B—

Class 1 Standard Stock Solution, *Class 1 Standard Solution*, *Class 2 Standard Stock Solutions*, *Class 2 Mixture A Standard Solution*, *Class 2 Mixture B Standard Solution*, *Test Stock Solution*, *Test Solution*, and *Class 1 System Suitability Solution*—Prepare as directed for *Procedure A*. ●₃

Chromatographic System (see *Chromatography* (621))—The gas chromatograph is equipped with a flame-ionization detector, a 0.32-mm × 30-m fused-silica column coated with a 0.25-μm layer of phase G16, or a 0.53-mm × 30-m wide-bore column coated with a 0.25-μm layer of phase G16. The carrier gas is nitrogen or helium with a linear velocity of about 35 cm per second and a split ratio of 1 : 5. ●[NOTE—Split ratio can be modified in order to optimize sensitivity.]●₃ The column temperature is maintained at 50° for 20 minutes, then raised at a rate of 6° per minute to 165°, and maintained at 165° for 20 minutes. The injection port and detector temperatures are maintained at 140° and 250°, respectively. Chromatograph the *Class 1 Standard Solution* and the *Class 1 System Suitability Solution*, ●₃ and record the peak responses as directed for *Procedure*: the signal-to-noise ratio of benzene in the *Class 1 Standard Solution* is not less than 5; the signal-to-noise ratio of each peak in the *Class 1 System Suitability Solution* is not less than 3; and the resolution, *R*, between acetonitrile and *cis*-dichloroethene in the *Class 2 Mixture A Standard Solution*●₃ is not less than 1.0.

Procedure—Separately inject (following one of the headspace operating parameter sets described in *Table 5*) equal volumes of headspace (about 1.0 mL) of the *Class 1 Standard Solution*, the *Class 2 Mixture A Standard Solution*, the *Class 2 Mixture B Standard Solution*, and the *Test Solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. If the peak response(s) in the *Test Solution* of the peak(s) identified in *Procedure A* is/are greater than or equal to a corresponding peak(s) in either the *Class 1 Standard Solution* or either of the two *Class 2 Mixture Standard Solutions*, proceed to *Procedure C* to quantify the peak(s); otherwise the article meets the requirements of this test.

Procedure C—

Class 1 Standard Stock Solution, *Class 1 Standard Solution*, *Class 2 Standard Stock Solution A*, *Class 2 Mixture A Standard Solution*, *Test Stock Solution*, *Test Solution*, and *Class 1 System Suitability Solution*—Prepare as directed for *Procedure A*.

Standard Solution—[NOTE—•Prepare a separate *Standard Solution* for each peak identified and verified by *Procedures A* and *B*. For the *Class 1* solvents other than 1,1,1-trichloroethane, prepare the first dilution as directed for the first dilution under *Class 1 Standard Stock Solution* in *Procedure A*.] Transfer an accurately measured volume of each individual USP Reference Standard corresponding to each residual solvent peak identified and verified by *Procedures A* and *B* to a suitable container, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having a final concentration of 1/20 of the value stated in *Table 1* or *2* (under *Concentration Limit*). Transfer 1.0 mL of this solution to an appropriate headspace vial, add 5.0 mL of water, apply the stopper, cap, and mix.

Spiked Test Solution—[NOTE—Prepare a separate *Spiked Test Solution* for each peak identified and verified by *Procedures A* and *B*.] Transfer 5.0 mL of *Test Stock Solution* to an appropriate headspace vial, add 1.0 mL of the *Standard Solution*, apply the stopper, cap, and mix.

Chromatographic System (see *Chromatography* (621))—[NOTE—If the results of the chromatography from *Procedure A* are found to be inferior to those found with *Procedure B*, the *Chromatographic System* from *Procedure B* may be substituted.] The gas chromatograph is equipped with a flame-ionization detector, a 0.32-mm × 30-m fused-silica column coated with a 1.8-μm layer of phase G43 or a 0.53-mm × 30-m wide-bore column coated with a 3.0-μm layer of phase G43. The carrier gas is nitrogen or helium with a linear velocity of about 35 cm per second, and a split ratio of 1 : 5. [NOTE—Split ratio can be modified in order to optimize sensitivity.] The column temperature is maintained at 40° for 20 minutes, then raised at a rate of 10° per minute to 240°, and maintained at 240° for 20 minutes. The injection port and detector temperatures are maintained at 140° and 250°, respectively. Chromatograph the *Class 1 Standard Solution*, the *Class 1 System Suitability Solution*, and the *Class 2 Mixture A Standard Solution*, and record the peak responses as directed for *Procedure*: the signal-to-noise ratio of 1,1,1-trichloroethane in the *Class 1 Standard Solution* is not less than 5; the signal-to-noise ratio of each peak in the *Class 1 System Suitability Solution* is not less than 3; and the resolution, *R*, between acetonitrile and methylene chloride in the *Class 2 Mixture A Standard Solution* is not less than 1.0.

Procedure—Separately inject (following one of the headspace operating parameters described in *Table 5*) equal volumes of headspace (about 1.0 mL) of the *Standard Solution*, the *Test Solution*, and the *Spiked Test Solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the amount, in ppm, of each residual solvent found in the article under test by the formula:

$$5(C/W)[r_U/(r_{ST} - r_U)]$$

in which *C* is the concentration, in μg per mL, of the appropriate USP Reference Standard in the *Standard Solution*; *W* is the weight, in g, of the article under test taken to prepare the *Test Stock Solution*; and *r_U* and *r_{ST}* are the peak responses of each residual solvent obtained from the *Test Solution* and the *Spiked Test Solution*, respectively.

WATER-INSOLUBLE ARTICLES

•**Procedure A**—[NOTE—Dimethyl sulfoxide may be substituted as an alternative solvent to dimethylformamide.]

Class 1 Standard Stock Solution—Transfer 1.0 mL of USP *Class 1 Residual Solvents Mixture RS* to a 100-mL volumetric flask previously filled with about 80 mL of dimethylformamide, dilute with dimethylformamide to volume, and mix. Transfer 1.0 mL of this solution to a 100-mL volumetric flask, previously filled with about 80 mL of dimethylformamide, dilute with dimethylformamide to volume, and mix. [NOTE—Reserve a portion of this solution for the *Class 1 System Suitability Solution*.] Transfer 1.0 mL of this solution to a 10-mL volumetric flask, dilute with dimethylformamide to volume, and mix.

Class 1 Standard Solution—Transfer 1.0 mL of *Class 1 Standard Stock Solution* to an appropriate headspace vial, containing 5.0 mL of water, apply the stopper, cap, and mix.

Class 2 Standard Stock Solutions—Transfer 1.0 mL of USP *Residual Solvents Class 2—Mixture A RS* to a 100-mL volumetric flask, previously filled with about 80 mL of dimethylformamide, dilute with dimethylformamide to volume, and mix. This is *Class 2 Standard Stock Solution A*. Transfer 0.5 mL of USP *Residual Solvents Class 2—Mixture B RS* to a 10-mL volumetric flask, dilute with dimethylformamide to volume, and mix. This is *Class 2 Standard Stock Solution B*.

Class 2 Mixture A Standard Solution—Transfer 1.0 mL of *Class 2 Standard Stock Solution A* to an appropriate headspace vial, containing 5.0 mL of water, apply the stopper, cap, and mix.

Class 2 Mixture B Standard Solution—Transfer 1.0 mL of *Class 2 Standard Stock Solution B* to an appropriate headspace vial, containing 5.0 mL of water, apply the stopper, cap, and mix.

Test Stock Solution—Transfer about 500 mg of the article under test, accurately weighed, to a 10-mL volumetric flask, dissolve in and dilute with dimethylformamide to volume, and mix.

Test Solution—Transfer 1.0 mL of the *Test Stock Solution* to an appropriate headspace vial, containing 5.0 mL of water, apply the stopper, cap, and mix.

Class 1 System Suitability Solution—Mix 5 mL of the *Test Stock Solution* with 0.5 mL of the intermediate dilution reserved from *Class 1 Standard Stock Solution*. Transfer 1.0 mL of this solution to an appropriate headspace vial, containing 5.0 mL of water, apply the stopper, cap, and mix.

Chromatographic System (see *Chromatography* (621))—The gas chromatograph is equipped with a flame-ionization detector, a 0.53-mm × 30-m wide-bore column coated with a 3.0-μm layer of phase G43. The carrier gas is helium with a linear velocity of about 35 cm per second, and a split ratio of 1 : 3. [NOTE—Split ratio can be modified in order to optimize sensitivity.] The column temperature is maintained at 40° for 20 minutes, then raised at a rate of 10° per minute to 240°, and maintained at 240° for 20 minutes. The injection port and detector temperatures are maintained at 140° and 250°, respectively. Chromatograph the *Class 1 Standard Solution*, *Class 1 System Suitability Solution*, and *Class 2 Mixture A Standard Solution*, and record the peak responses as directed for *Procedure*: the signal-to-noise ratio of 1,1,1-trichloroethane in the *Class 1 Standard Solution* is not less than 5; the signal-to-noise ratio of each peak in the *Class 1 System Suitability Solution* is not less than 3; and the resolution, *R*, between acetonitrile and methylene chloride in the *Class 2 Mixture A Standard Solution* is not less than 1.0.

Procedure—Separately inject (use headspace operating parameters 3 in *Table 5* with a vial pressure of 10 psi) equal volumes of headspace (about 1.0 mL) of the *Class 1 Standard Solution*, *Class 2 Mixture A Standard Solution*, *Class 2 Mixture B Standard Solution*, and the *Test Solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. If a peak response of any peak, other than a peak for 1,1,1-trichloroethane, in the *Test Solution* is greater than or equal to a corresponding peak in either the *Class 1 Standard Solution* or either of the two *Class 2 Mixture Standard Solutions*, or a peak response of 1,1,1-trichloroethane is greater than or equal to 150 times the peak response corresponding to 1,1,1-trichloroethane in the *Class 1 Standard Solution*, proceed to *Procedure B* to verify the identity of the peak; otherwise the article meets the requirements of this test.

Procedure B—

Class 1 Standard Stock Solution, Class 1 Standard Solution, Class 1 System Suitability Solution, Class 2 Standard Stock Solutions, Class 2 Mixture A Standard Solution, and Class 2 Mixture B Standard Solution, Test Stock Solution, and Test Solution—Proceed as directed for Procedure A.

Chromatographic System—Proceed as directed for Procedure B under *Water-Soluble Articles* with a split ratio of 1 : 3. [NOTE—Split ratio can be modified in order to optimize sensitivity.]

Procedure—Separately inject (use headspace operating parameters 3 in Table 5 with a vial pressure of 10 psi) equal volumes of headspace (about 1.0 mL) of the *Class 1 Standard Solution, Class 2 Mixture A Standard Solution, Class 2 Mixture B Standard Solution, and the Test Solution*, into the chromatograph, record the chromatograms, and measure the responses for the major peaks. If the peak response(s) in the *Test Solution* of the peak(s) identified in Procedure A is/are greater than or equal to a corresponding peak(s) in either the *Class 1 Standard Solution* or any of the two *Class 2 Mixture Standard Solutions*, proceed to Procedure C to quantify the peak(s); otherwise the article meets the requirements of this test.

Procedure C—

Class 1 Standard Stock Solution, Class 1 Standard Solution, Class 1 System Suitability Solution, Class 2 Standard Stock Solution A, and Class 2 Mixture A Standard Solution—Proceed as directed for Procedure A.

Standard Stock Solution—[NOTE—Prepare a separate Standard Solution for each peak identified and verified by Procedures A and B.] Transfer an accurately measured volume of each individual USP Reference Standard corresponding to each residual solvent peak identified and verified by Procedures A and B to a suitable container, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having a final concentration of 1/20 of the value stated in Table 1 or Table 2 (under *Concentration Limit*).

Standard Solution—Transfer 1.0 mL of the *Standard Stock Solution* to an appropriate headspace vial, containing 5.0 mL of water, apply the stopper, cap, and mix.

Test Stock Solution—Proceed as directed for Procedure A.

Test Solution—Transfer 1.0 mL of the *Test Stock Solution* to an appropriate headspace vial, containing 5.0 mL of water, apply the stopper, cap, and mix.

Spiked Test Solution—[NOTE—Prepare a separate *Spiked Test Solution* for each peak identified and verified by Procedures A and B.] Transfer 1.0 mL of the *Test Stock Solution* to an appropriate headspace vial, add 1 mL of the *Standard Stock Solution* and 4.0 mL of water, apply the stopper, cap, and mix.

Chromatographic System—Proceed as directed for Procedure C under *Water-Soluble Articles*.

Procedure—Separately inject (use headspace operating parameters 3 in Table 5 with a vial pressure of 10 psi) equal volumes of headspace (about 1.0 mL) of the *Standard Solution, the Test Solution, and the Spiked Test Solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the amount, in ppm, of each residual solvent found in the article under test by the formula:

$$10(C/W)[r_U / (r_{ST} - r_U)]$$

in which *C* is the concentration, in µg per mL, of the appropriate USP Reference Standard in the *Standard Solution*; *W* is the weight, in g, of the article under test taken to prepare the *Test Stock Solution*; and *r_U* and *r_{ST}* are the peak responses of each residual solvent obtained from the *Test Solution* and the *Spiked Test Solution*, respectively.

Class 3 Residual Solvents

• If Class 3 solvents are present, the level of residual solvents may be determined as directed under *Loss on Drying* (731) when the monograph for the article under test contains a loss on drying procedure, or a specific determination of the solvent may be made. If there is no loss on drying procedure in the monograph for the article under test or if a Class 3 solvent limit in an individual monograph is greater than 50 mg per day (corresponding to 5000 ppm or 0.5% under Option 1), the individual Class 3 residual solvent or solvents present in the article under test, should be identified and quantified, and the procedures as described above, with appropriate modifications to the standard solutions, are to be applied wherever possible. Otherwise an appropriate validated procedure is to be employed. • USP Reference Standards, where available, should be used in these procedures. A flow diagram for the application of residual solvent limit tests is shown in Figure 1.

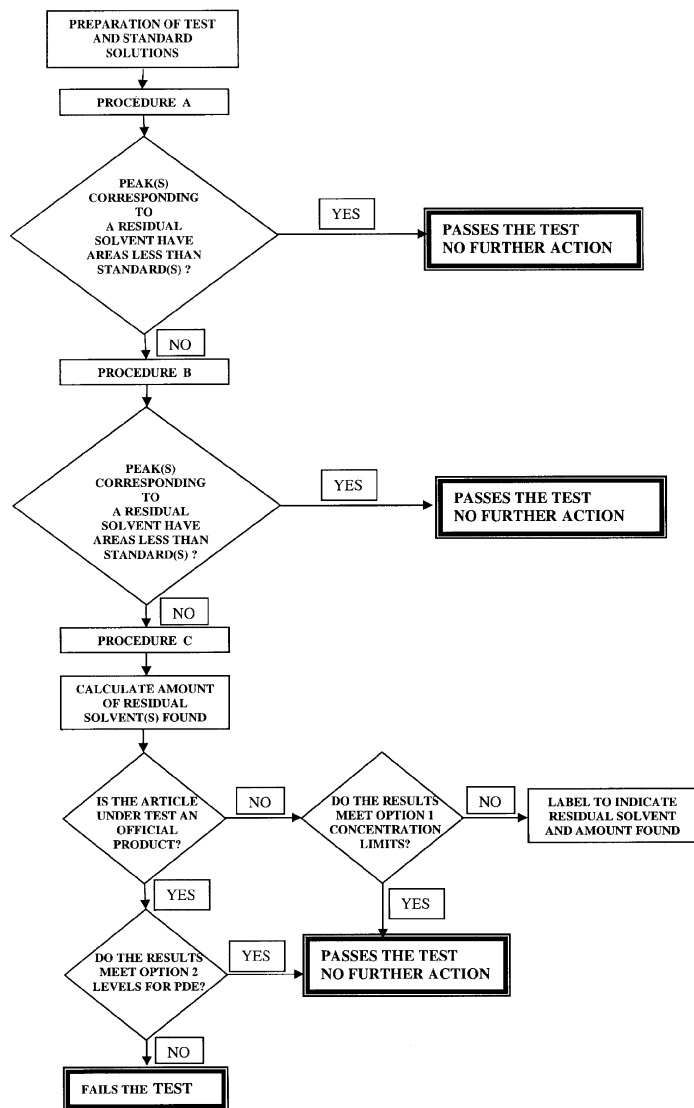


Figure 1. Diagram relating to the identification of residual solvents and the application of limit tests.