

## <467> RESIDUAL SOLVENTS

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### 1. INTRODUCTION

For pharmacopeial purposes, residual solvents in pharmaceuticals are defined as organic volatile chemicals that are used or produced in the manufacturing of drug substances, excipients, or dietary ingredients, or in the preparation of drug products or dietary supplement products. Appropriate selection of the solvent for the synthesis of a drug substance or an excipient may enhance the yield or determine characteristics such as crystal form, purity, and solubility. Therefore, the solvent may sometimes be a critical element in the synthetic process and may not be completely removed by the manufacturing process. Because residual solvents do not provide therapeutic benefit, they should be removed, to the extent possible, to meet safety-based limits, ingredient and product specifications, good manufacturing practices, or other quality-based requirements.

The objective of this general chapter is to define acceptable amounts of residual solvents in pharmaceutical drug products and dietary supplement products for the safety of the patient. Tests for residual solvents are not generally mentioned in specific monographs because the solvents used may vary from one manufacturer to another; however, the limits to be applied must comply with those specified in this general chapter.

This chapter provides procedures for the analysis of residual solvents, although alternative validated methodologies may also be used to demonstrate compliance with the defined limits. For guidance on verification of USP procedures or validation of alternative methods for residual solvents, see *Residual Solvents—Verification of Compendial Procedures and Validation of Alternative Procedures* (1467). This chapter does not address solvents deliberately used as excipients, nor does it address solvents. The limits specified in this chapter do not apply directly to excipients, drug substances, or dietary ingredients except where specified in the individual monographs. However, residual solvent levels present in drug substances, excipients, and dietary ingredients may be used to demonstrate compliance as an integral part of the control strategy, thereby reducing or eliminating the need for analysis in the product (see 3. *Control Strategy*).

Information on residual solvents in coating materials, colorants, flavors, capsules, and imprinting inks is generally not needed unless Class 1 solvents are used in the manufacture of these components.

Throughout this chapter, the term “likely to be present” (LTBP) refers to 1) solvents used or produced in the final manufacturing step; 2) solvents used or produced in earlier manufacturing steps that are not consistently removed by a validated process; and 3) solvents properly declared by a validated supplier of a drug substance, excipient, or dietary ingredient.

### 2. CLASSIFICATION OF RESIDUAL SOLVENTS BY RISK ASSESSMENT

Residual solvents assessed in this general chapter are listed in *Appendix 1* by common names and structures. USP is aligned with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for

Human Use (ICH) Harmonised Tripartite Guideline for Residual Solvents Q3C (F5) approach for the classification of residual solvents (see *Appendix 2* for additional details). These solvents were evaluated for their possible risk to human health and were placed into one of three classes based on their toxicity data and their environmental impact as shown in *Table 1*.

Table 1. Classification of Residual Solvents and Their Assessments

Residual Solvent Classes	Assessment
Class 1 (solvents to be avoided)	Known human carcinogens
	Strongly suspected human carcinogens
	Solvents particularly known to have ozone-depleting properties
Class 2 (solvents to be limited)	Nongenotoxic animal carcinogens or possible causative agents of other irreversible toxicity, such as neurotoxicity or teratogenicity
	Solvents suspected of other significant but reversible toxicities
Class 3 (solvents with low toxic potential)	Solvents with low toxic potential to humans; no health-based exposure limit is needed

The limits for Class 2 solvents are based on the toxicological permitted daily exposure (PDE), calculated as defined in *Appendix 3*, whereas Class 3 solvents are considered less toxic, and control to 50 mg/day or less for each of these solvents is acceptable without justification. The lists in this chapter are not exhaustive and are subject to revision. For solvents not listed, *Appendix 3* may be used to define PDE limits if sufficient toxicological data are available. A flow diagram for potential sources of residual solvents in pharmaceutical drug products and dietary supplements is shown in *Figure 1*.

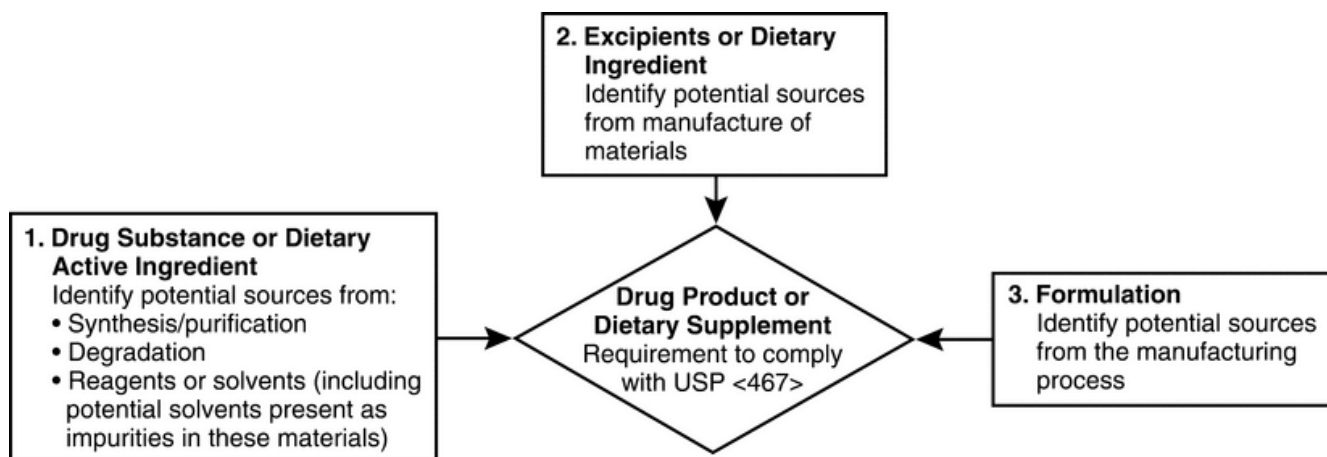


Figure 1. Potential sources of residual solvents in pharmaceutical drug products and dietary supplements.

There are three potential sources of residual solvents in the pharmaceutical drug products and dietary supplement products that should be considered (see *Figure 1*):

1. Drug substance or dietary active ingredient
  - Potential solvent sources include their use or formation during the synthesis or purification of the drug substance; their presence in raw materials or reagents used in their synthesis; or degradation of the drug substance.
2. Excipients and/or dietary ingredient
  - Potential solvent sources include their use or formation during the manufacture or purification of excipients.
3. Formulation
  - Potential solvent sources are associated with their use or formation during the official product manufacturing process.

The potential presence of other solvents as impurities in the solvents used must be taken into consideration in the assessment of solvents LTBP. Because of the high toxicity of benzene and other Class 1 solvents, all likely sources of these solvents must be considered. For example, potential sources of benzene may include its presence as an impurity in a solvent used in the manufacturing process; its use in the manufacture of starting material; or its production as a reaction by-product. In the event that the user has insufficient information to complete a thorough assessment of the potential sources of residual solvents (or as an alternative to performing this assessment), solvent screening may be used (see 8. *Analytical Procedures for Class 1 and Class 2 Residual Solvents*).

Pharmaceutical drug products and dietary supplement products should contain no higher levels of residual solvents than can be supported by safety data. All solvents included in this general chapter are listed in *Appendix 1*. Those solvents that show toxicity of special concern or carcinogenicity, and/or atmospheric ozone-depletion effects (Class 1, see *Table 2*), should be avoided in the production of drug substances, dietary supplement ingredients, excipients, pharmaceutical drug products, and dietary supplement products unless their use can be strongly justified in a risk-benefit assessment. Those solvents associated with less severe but still significant toxicity (Class 2, see *Table 3*) should be limited to protect patients from potential adverse effects. Whenever it is practicable, less toxic solvents (Class 3, see *Table 4*) should be used. For the purposes

of this pharmacopeia, when a manufacturer has received approval from a regulatory authority for the use of a solvent not currently listed in this chapter, or for a level of a listed solvent higher than the limit currently given in this chapter, it is the responsibility of that manufacturer to notify USP of the identity and level of the solvent, and the appropriate test procedure. USP will then address the information in the individual monograph. A new solvent or revised limit that has been approved through the ICH process will be added to the appropriate list in this general chapter. See *Appendix 2* for additional background information related to residual solvents.

### 3. CONTROL STRATEGY

The user may choose to demonstrate compliance with this chapter by analysis for residual solvents in the official product or by analysis of the official substances. These control strategy options are presented in *Figure 2*.

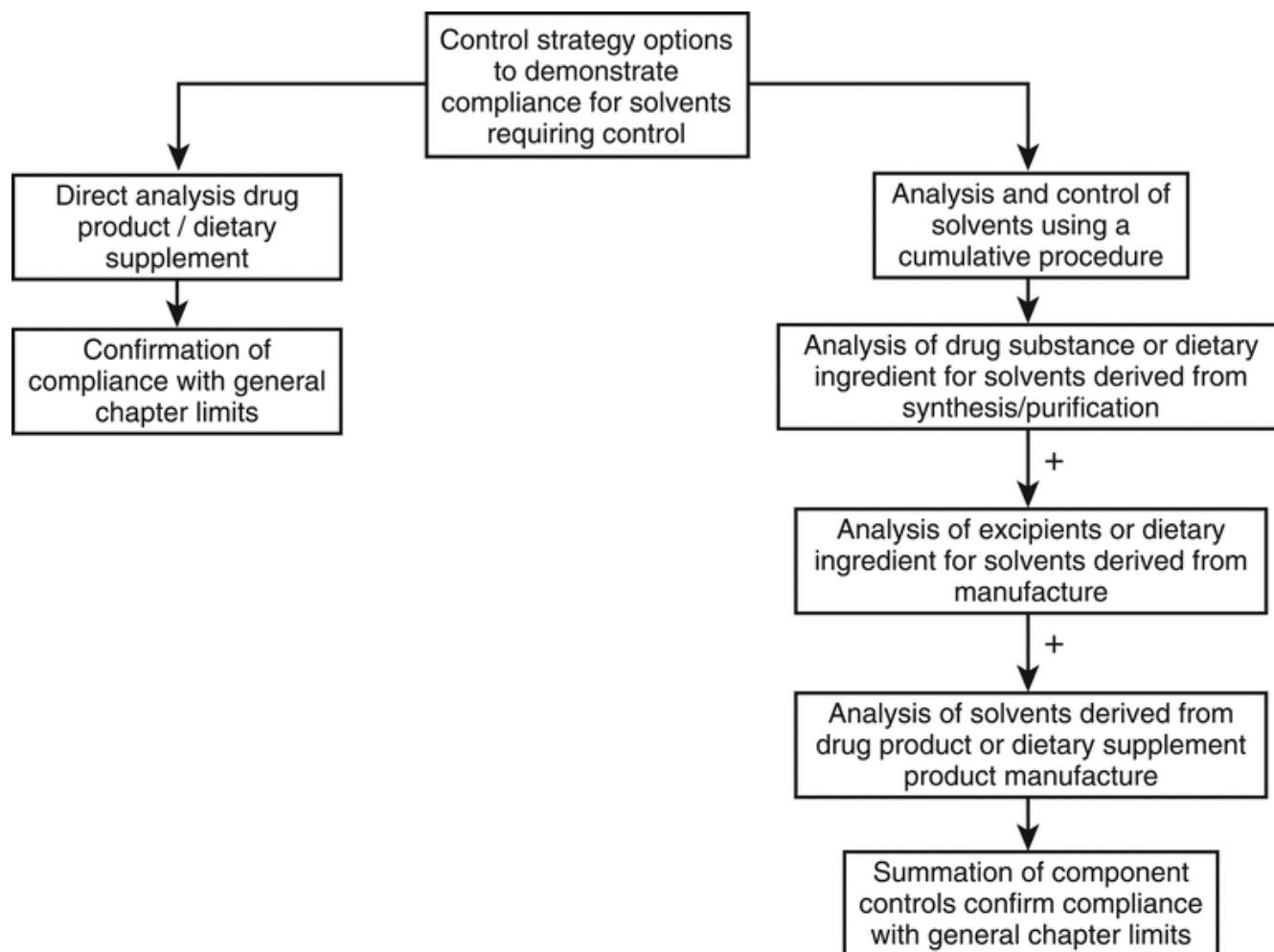


Figure 2. Control strategy options.

Compliance with the chapter requires that all solvents LTBP comply with the control limits. The following options are to be considered when designing the control strategy.

1. Testing the official product: This approach is acceptable in all cases.
2. Analysis of the official substances and using a cumulative approach to determine the solvent content in the official product:
  - A. If no solvent(s) are used during the manufacture of the official product, use the cumulative approach to determine the solvent content in the active pharmaceutical ingredient (API) and excipients or dietary ingredients to calculate solvent levels in the official product.
  - B. If solvent(s) are used during the manufacture of the official product, use the cumulative approach as described in (a) above. Then, for each solvent used in the manufacture, determine the content in the finished product or after the manufacturing step where the solvent(s) were used.

In all cases, the solvent levels in the final official product must not exceed the limits defined in the chapter.

Change to read:

## 4. LIMITS OF RESIDUAL SOLVENTS

## 4.1 Class 1: Solvents to Be Avoided

Class 1 residual solvents (*Table 2*) should not be used in the manufacture of drug substances, excipients, dietary ingredients, or official products because of their unacceptable toxicities or deleterious environmental effects. However, if their use in order to produce an official product with a significant therapeutic advance is unavoidable, their levels should be restricted as shown in *Table 2*, unless otherwise stated in the individual monograph. The solvent 1,1,1-trichloroethane is included in *Table 2* because it is a severe environmental hazard. The stated limit of 1500 ppm is based on a review of safety data.

The procedures described in 7. *Identification, Control, and Quantification of Residual Solvents* in this general chapter are to be applied wherever possible. Otherwise an appropriate validated procedure is to be used.

Table 2. Control Limits for Class 1 Residual Solvents in Official Products: Solvents to Be Avoided

Solvent	Concentration Limit (ppm)	Concern
Benzene	2	Carcinogen
Carbon tetrachloride	4	Toxic and environmental hazard
1,2-Dichloroethane	5	Toxic
1,1-Dichloroethene	8	Toxic
1,1,1-Trichloroethane	1500	Environmental hazard

## 4.2 Class 2: Solvents to Be Limited

Class 2 residual solvents (*Table 3*) should be limited in drug substances, excipients, dietary ingredients, and official products because of the inherent toxicities of these residual solvents. PDEs are given to the nearest 0.1 mg/day, and concentrations are given to the nearest 10 ppm. The method used to establish PDEs for residual solvents is presented in *Appendix 3*.

Table 3. Class 2 Residual Solvents in Official Products

Solvent	PDE (mg/day)	Concentration Limit (ppm)
Acetonitrile	4.1	410
Chlorobenzene	3.6	360
Chloroform	0.6	60
Cumene	0.7	70
Cyclohexane	38.8	3880
1,2-Dichloroethene	18.7	1870
1,2-Dimethoxyethane	1.0	100
<i>N,N</i> -Dimethylacetamide	10.9	1090
<i>N,N</i> -Dimethylformamide	8.8	880
1,4-Dioxane	3.8	380
2-Ethoxyethanol	1.6	160
Ethylene glycol	6.2	620
Formamide	2.2	220
Hexane	2.9	290
Methanol	30.0	3000
2-Methoxyethanol	0.5	50
Methylbutylketone	0.5	50
Methylcyclohexane	11.8	1180
Methylene chloride	6.0	600
▲Methylisobutylketone	45	4500▲ (Official 1-Dec-2020)
<i>N</i> -Methylpyrrolidone	5.3	530

Table 3. Class 2 Residual Solvents in Official Products (*continued*)

Solvent	PDE (mg/day)	Concentration Limit (ppm)
Nitromethane	0.5	50
Pyridine	2.0	200
Sulfolane	1.6	160
Tetrahydrofuran	7.2	720
Tetralin	1.0	100
Toluene	8.9	890
Trichloroethylene	0.8	80
Xylene <sup>a</sup>	21.7	2170

<sup>a</sup> Usually 60% *m*-xylene, 14% *p*-xylene, and 9% *o*-xylene with 17% ethyl benzene.

### 4.3 Class 3: Solvents with Low Toxic Potential

Class 3 solvents (*Table 4*) are regarded as less toxic and of lower risk to human health than Class 1 and Class 2 residual solvents. Class 3 includes no solvent known to be a human health hazard at levels normally accepted in pharmaceuticals. However, there are no long-term toxicity or carcinogenicity studies for many of the residual solvents in Class 3. Available data indicate that they are less toxic in acute or short-term studies and negative in genotoxicity studies.

It is considered that amounts of these residual solvents of 50 mg/day or less of each solvent (corresponding to 5000 ppm or 0.5% w/w in *Option 1*, which is described below) would be acceptable for each solvent without justification. Higher amounts may also be acceptable, provided that they are realistic in relation to manufacturing capability and good manufacturing practice. If a Class 3 solvent limit in an individual monograph is greater than 0.5%, that residual solvent should be identified and quantified. The procedures described in *7. Identification, Control, and Quantification of Residual Solvents*, with appropriate modifications to the standard solutions, are to be applied wherever possible. Otherwise, an appropriate validated procedure is to be used.

Table 4. Class 3 Residual Solvents in Official Products

Acetic acid	Isobutyl acetate
Acetone	Isopropyl acetate
Anisole	Methyl acetate
1-Butanol	3-Methyl-1-butanol
2-Butanol	Methylethylketone
Butyl acetate	▲▲ (Official 1-Dec-2020)
<i>tert</i> -Butylmethyl ether	2-Methyl-1-propanol
Dimethyl sulfoxide	Pentane
Ethanol	1-Pentanol
Ethyl acetate	1-Propanol
Ethyl ether	2-Propanol
Ethyl formate	Propyl acetate
Formic acid	▲Triethylamine▲ (Official 1-Dec-2020)
Heptane	

## 5. OPTIONS FOR DESCRIBING LIMITS OF CLASS 2 AND CLASS 3 RESIDUAL SOLVENTS

This chapter provides two options for establishing compliance. Both *Option 1* and *Option 2* are based on the PDE

### 5.1 Option 1—Concentration Limit

The concentration limits in ppm stated in *Table 3* for Class 2 solvents and the general requirement for Class 3 (5000 ppm, equivalent to 0.5% w/w) are used. The values for Class 2 solvents were calculated using the equation below by assuming a product weight of 10 g administered daily.

$$\text{Concentration (ppm)} = (1000 \mu\text{g}/\text{mg} \times \text{PDE})/\text{dose}$$

Here, PDE is given in terms of milligrams per day (mg/day), and dose is given in grams per day (g/day). These limits are considered acceptable for all drug substances, excipients, dietary ingredients, and official products. Therefore, *Option 1* may be applied if the daily amount is not known or does not exceed 10 g. If all official substances (drug substances, excipients, and/or dietary ingredients) in a formulation or dietary supplement meet the limits given in *Option 1*, these components may be used in any proportions. No further calculation is necessary, provided that the daily amount does not exceed 10 g. Products that are administered in doses (daily intake for dietary supplements) greater than 10 g/day are to be considered under *Option 2*.

## 5.2 Option 2—Summation of Components Content

*Option 2* uses the PDE and the actual maximum daily amount of the product to calculate solvent exposure and assess compliance.

*Option 2* must be used to demonstrate compliance with this chapter where the maximum daily dose of the official product exceeds 10 g/day or where at least one component in the formulation exceeds the *Option 1* limits.

These limits are applied by summing the amounts of a residual solvent present in each of the components of the official product. The contribution of each solvent per day should result in a total amount that does not exceed the PDE.

Consider the example of the application of *Option 1* and *Option 2* limits to acetonitrile concentration in an official product. The PDE for acetonitrile is 4.1 mg/day, thus the *Option 1* limit is 410 ppm. The maximum administered daily mass of an official product is 5.0 g, and the official product contains two excipients. Assuming that there is no other source of acetonitrile in the manufacturing process, the calculated official product content of acetonitrile and the daily exposure are given in *Table 5*.

Table 5. Example of Meeting the Requirement for Acetonitrile as per Option 2

Component	Amount in Formulation (g)	Acetonitrile Content (ppm)	Daily Exposure (mg)
Drug substance	0.3	800	0.24
Excipient 1	0.9	400	0.36
Excipient 2	3.8	800	3.04
Official product	5.0	728	3.64

*Excipient 1* meets the *Option 1* limit, but the official substance, *Excipient 2*, and *Official product* do not meet the *Option 1* limit. Nevertheless, the product meets the *Option 2* limit of 4.1 mg/day and thus conforms to the recommendations in this chapter.

Consider another example using acetonitrile as a residual solvent. The maximum administered daily mass of an official product is 5.0 g, and the official product contains two excipients. Assuming no other source of acetonitrile in the manufacturing process, the *Official product's* content of acetonitrile and the maximum content of residual acetonitrile are given in *Table 6*.

Table 6. Example of Failing the Requirement for Acetonitrile as per Option 2

Component	Amount in Formulation (g)	Acetonitrile Content (ppm)	Daily Exposure (mg)
Drug substance	0.3	800	0.24
Excipient 1	0.9	2000	1.8
Excipient 2	3.8	800	3.04
Official product	5.0	1016	5.08

In this example, the product meets neither the *Option 1* nor the *Option 2* limit according to the summation. Compliance with the chapter may still be demonstrated via analysis of the *Official product* as it is possible that the formulation process may have reduced the level of acetonitrile below the calculated content. If the level of acetonitrile was not reduced during formulation to the allowed limit, then the manufacturer of the *Official product* should take other steps to reduce the amount of acetonitrile in the official product. If the manufacturer receives approval from the regulatory authority for such a higher level of residual solvent, it is the responsibility of that manufacturer to notify USP regarding the identity of this solvent and the approved residual solvent limit in the article. USP will then address this topic in the individual monograph.

## 6. REPORTING LEVELS OF RESIDUAL SOLVENTS

Manufacturers of pharmaceutical products need certain information about the content of residual solvents in drug substances and excipients to meet the criteria of this chapter. The following statements are given as acceptable examples of the information that could be provided from a supplier of drug substances or excipients to a pharmaceutical manufacturer. The supplier might choose one of the following as appropriate:

- If Class 1 solvents are present, they should be identified and quantified.

- Only Class 2 solvents X, Y, ... are LTBP. All are below the *Option 1* limit. (Here the supplier would name the Class 2 solvents represented by X, Y, ...)
- Only Class 2 solvents X, Y, ..., and Class 3 solvents are LTBP. Residual Class 2 solvents are below the *Option 1* limit and residual Class 3 solvents are below 0.5% each.
- Only Class 3 solvents are LTBP. Loss on drying (LOD) is not greater than 0.5%.
- If only Class 3 solvents are LTBP and LOD is more than 0.5%, they should be identified and quantified.
- If solvents of Class 2 or Class 3 are present at greater than their *Option 1* limits or 0.5%, respectively, they should be identified and quantified to allow compliance with *Option 2*.

The term LTBP as used in the above examples refers to the solvent used or produced in the final manufacturing step and to solvents used or produced in earlier manufacturing steps and not removed consistently by a validated process.

## 7. IDENTIFICATION, CONTROL, AND QUANTIFICATION OF RESIDUAL SOLVENTS

Whenever possible, the substance under test needs to be dissolved to release the residual solvent. The control strategy may involve analysis of official products, active ingredients, excipients, and dietary ingredients. In some cases the sample does not dissolve completely. In such cases it may be acceptable to pulverize the sample into a fine powder carefully, avoiding the generation of frictional heat and in a manner that minimizes the loss of volatile solvents. This technique ensures that any residual solvent that may be present can be released. It should be performed as fast as possible immediately prior to dispersion in the sample solvent, to minimize the loss of volatile solvents during the procedure.

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

### 7.1 Class 1 and Class 2 Residual Solvents

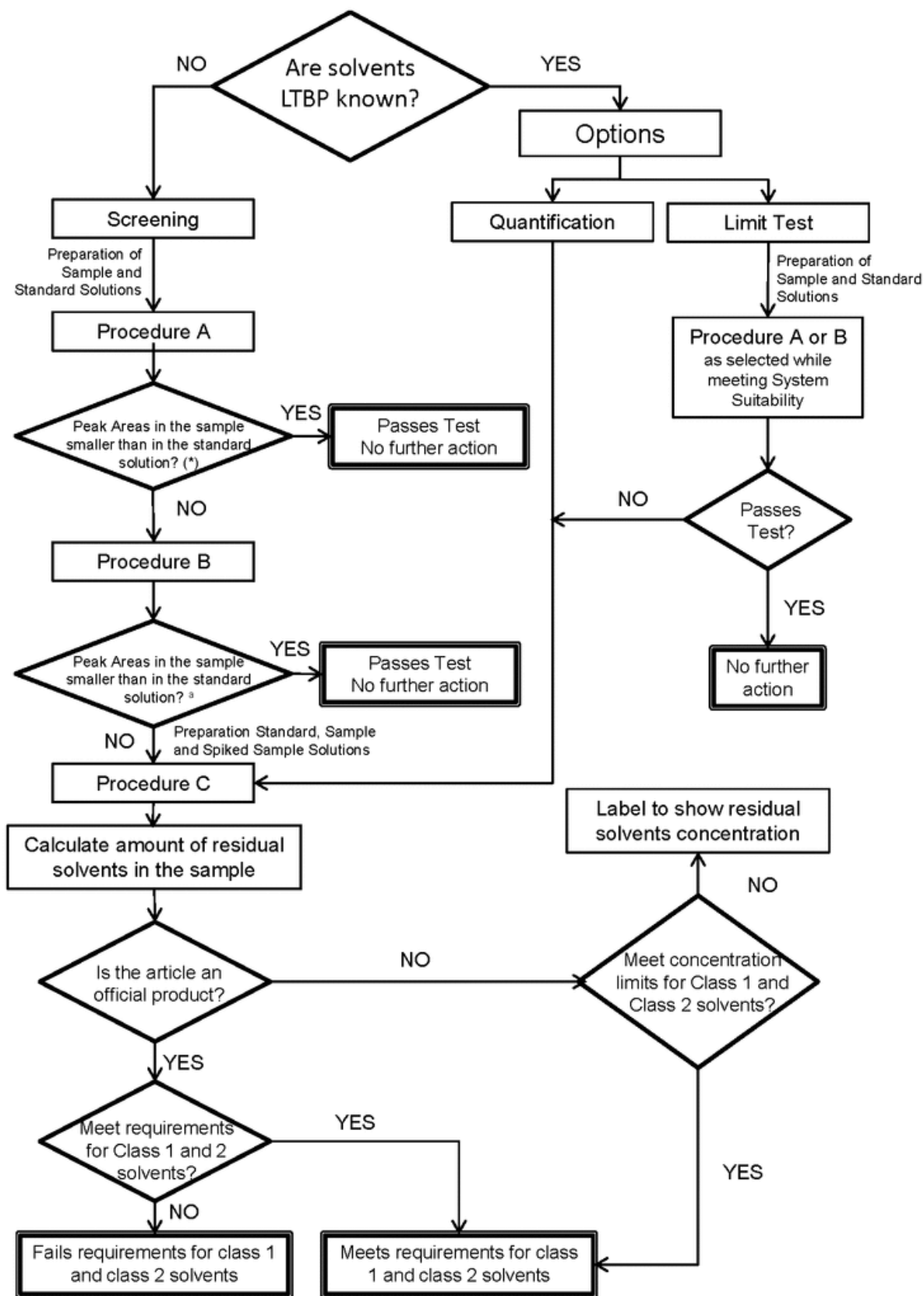
This chapter describes analytical procedures (*Procedures A, B, and C*) for evaluating the levels of all Class 1 and the majority of Class 2 residual solvents. For each test matrix, verification is needed to demonstrate reliability of the compendial procedure, as described in (1467).

When the solvents that are present or potentially present in the sample are known, they can be determined using a limit test such as *Procedure A* or *Procedure B*, or by a quantitative test, such as *Procedure C*.

When the solvents LTBP are not known, use the screening tests of *Procedure A* and *Procedure B* as required. *Procedure A* and *Procedure B* can separate most of the solvents listed in this chapter. Additionally, *Figure 3* can be used as a decision tree to demonstrate compliance.

In a screening test, if the article does not meet the acceptance criteria of *Procedure A*, then *Procedure B* is to be used to demonstrate compliance. If the article does not meet the criteria using *Procedure A* and *Procedure B*, then *Procedure C* must be used to quantify the residual solvent(s) present in the article.

When the information about solvents LTBP in the material is known, the system suitability requirements only need to be demonstrated for the solvents expected to be present. Several residual solvents listed in this chapter are not detected at the limit concentration using the analytical procedure described below. Those solvents include formamide, 2-ethoxyethanol, 2-methoxyethanol, ethylene glycol, *N*-methylpyrrolidone, sulfolane, *N,N*-dimethylacetamide, and *N,N*-dimethylformamide. Those solvents should be determined using an alternative method that has been appropriately validated to demonstrate that the method is suitable for its intended purpose, i.e., quantitative determination of residual solvent or limit tests for them (see *Category II* in *Validation of Compendial Procedures* (1225), *Table 2*, which provides definitions and general guidance on analytical procedures validation without indicating specific validation criteria for each characteristic). Chapter (1467) provides additional guidance on the specific validation criteria for alternative methods used for identification and quantification of residual solvents.



<sup>a</sup> Except 1,1,1-trichloroethane (TCE), which should be smaller than 150 times the size of the corresponding peak response from the Class 1 standard solution.

Figure 3. Determination of residual solvents and decision tree using *Procedures A, B, and C*.



## 7.2 Class 3 Residual Solvents

Procedures A and B can separate most solvents in Classes 1, 2, and 3. However, the procedures have not been validated for Class 3 solvents, and appropriate validation will be required (see the entry for alternative methods under 7.1 Class 1 and Class 2 Residual Solvents).

Change to read:

## 8. ANALYTICAL PROCEDURES FOR CLASS 1 AND CLASS 2 RESIDUAL SOLVENTS

### 8.1 Chromatographic Systems

(See *Chromatography* (621), *System Suitability* and *Figure 4*.)

#### PROCEDURE A

Mode: GC

Injector: Headspace (see *Table 9* for headspace settings)

Injection type: Split ratio, 1:5. [NOTE—Split ratio can be modified to optimize sensitivity.]

Detector: Flame ionization

Column: 0.32-mm × 30-m capillary fused silica coated with 1.8- $\mu$ m layer of phase G43 or 0.53-mm × 30-m wide-bore coated with a 3.0- $\mu$ m layer of phase G43

Column temperature: See *Table 7*.

Table 7. Procedure A Column Temperature

Initial Temperature (°)	Temperature Ramp (°/min)	Final Temperature (°)	Hold Time at Final Temperature (min)
40	0	40	20
40	10	240	—
240	0	240	20

Temperatures

Injection port: 140°

Detector: 250°

Carrier gas: Helium, nitrogen, or hydrogen

Linear velocity: About 35 cm/s for helium (adjustment and verification are necessary for other carrier gases)

#### PROCEDURE B

Mode: GC

Injector: Headspace (see *Table 9* for headspace settings)

Injection type: Split ratio, 1:5. [NOTE—Split ratio can be modified to optimize sensitivity.]

Detector: Flame ionization

Column: 0.32-mm × 30-m fused-silica coated with a 0.25- $\mu$ m layer of phase G16 or a 0.53-mm × 30-m wide-bore coated with a 0.25- $\mu$ m layer of phase G16

Column temperature: See *Table 8*.

Table 8. Procedure B Column Temperature

Initial Temperature (°)	Temperature Ramp (°/min)	Final Temperature (°)	Hold Time at Final Temperature (min)
50	0	50	20
50	6	165	—
165	0	165	20

Temperatures

Injection port: 140°

Detector: 250°

Carrier gas: Helium, nitrogen, or hydrogen

Linear velocity: About 35 cm/s for helium (adjustment and verification are necessary for other carrier gases)

## PROCEDURE C

Use the chromatographic conditions, from either *Procedure A* or *Procedure B*, that provide the best performance for the solvent(s) being tested.

## HEADSPACE PARAMETER SETTINGS

There are three general sets of headspace operating parameters that are used for *Procedures A* and *B* (Table 9).

Table 9. Headspace Operating Parameters

Procedure Parameters	Headspace Instrumental Setting		
	Set 1	Set 2	Set 3
Equilibration temperature (°)	80	105	80
Equilibration time (min)	60	45	45
Transfer-line temperature (°) [if appropriate] <sup>a</sup>	85	110	105
Syringe temperature (°) [if appropriate]	80–90	105–115	80–90
Carrier gas: helium, nitrogen, <sup>b</sup> or hydrogen <sup>b</sup> at an appropriate pres- sure <sup>b</sup>	—	—	—
Pressurization time(s) (sec) [if appro- priate]	≥60	≥60	≥60
Injection volume (mL) <sup>c</sup>	1	1	1

<sup>a</sup> It is recommended to increase the temperature of the transfer line between runs to eliminate any potential condensation of solvents.

<sup>b</sup> The use of nitrogen or hydrogen as the carrier gas requires adjustment and verification.

<sup>c</sup> Injection volume may be expressed in terms of the injection time.

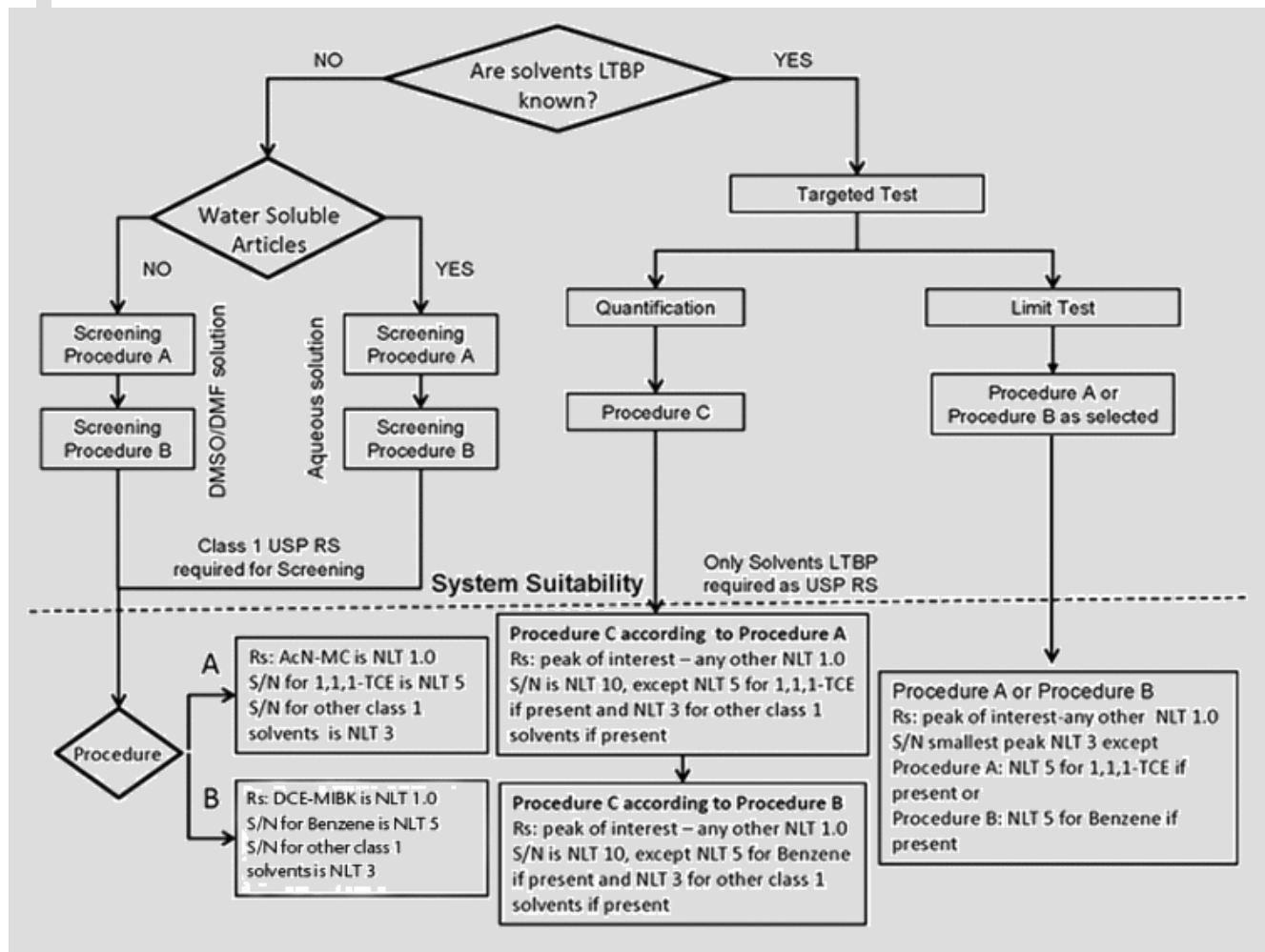


Figure 4. System suitability requirements based on the method of choice and previous knowledge about solvents LTBP. The acceptance criteria are based on the solvents LTBP (AcN: acetonitrile; 1,1,1-TCE: 1,1,1-trichloroethane; DCE: *cis*-dichloroethene; MC: methylene chloride; MIBK: Methylisobutylketone). ▲ (IFRA 1-Nov-2019)

## 8.2 Screening of Water-Soluble Articles

### STOCK SOLUTIONS

**Class 1 standard stock solution:** [NOTE—When transferring solutions, place the tip of the pipet just below the surface of the liquid and mix.] Transfer 1.0 mL of USP Residual Solvents Mixture—Class 1 RS to a 100-mL volumetric flask containing about 9 mL of dimethylsulfoxide, dilute with water to volume, and mix. Transfer 1.0 mL of this solution to a 100-mL volumetric flask containing about 50 mL of water, dilute with water to volume, and mix. Transfer 10 mL of this solution to a 100-mL volumetric flask containing about 50 mL of water, dilute with water to volume, and mix.

**Class 2 mixture A standard stock solution:** 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.

**Class 2 mixture B standard stock solution:** 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.

**Sample 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.

### SYSTEM SUITABILITY SOLUTION

**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 *Sample stock solution*, apply the stopper, cap, and mix.

## STANDARD SOLUTIONS

Class 1 standard solution: [NOTE—When transferring solutions, place the tip of the pipet just below the surface of the liquid and mix.] 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 mixture A standard solution: Transfer 1.0 mL of *Class 2 mixture A standard stock solution* to an appropriate headspace vial containing 5.0 mL of water, apply the stopper, cap, and mix.

Class 2 mixture B standard solution: Transfer 5.0 mL of *Class 2 mixture B standard stock solution* to an appropriate headspace vial, add 1.0 mL of water, apply the stopper, cap, and mix.

## SAMPLE SOLUTION

Sample solution: Transfer 5.0 mL of *Sample stock solution* to an appropriate headspace vial, add 1.0 mL of water, apply the stopper, cap, and mix.

## PROCEDURE A

Analysis: Using *Procedure A Chromatographic System*, separately inject (using one of the headspace operating parameter sets described in *Table 9*) equal volumes of headspace of the *Class 1 standard solution*, *Class 1 system suitability solution*, *Class 2 mixture A standard solution*, *Class 2 mixture B standard solution*, and *Sample solution* into the chromatograph, record the chromatograms, and measure the responses for the peaks of interest.

System suitability requirements (see *Figure 4*): The signal-to-noise (S/N) ratio for 1,1,1-trichloroethane in the *Class 1 standard solution* is NLT 5. The S/N ratio of each peak in the *Class 1 system suitability solution* is NLT 3, and the resolution between acetonitrile and methylene chloride in the *Class 2 mixture A standard solution* is NLT 1.0.

Acceptance criteria: If a response of any peak, other than the peak for 1,1,1-TCE, in the *Sample solution* is greater than or equal to a corresponding peak in either the *Class 1 standard solution*, or either *Class 2 mixture A standard solution* or *Class 2 mixture B standard solution*, 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

Analysis: Using *Procedure B Chromatographic System*, separately inject (using one of the headspace operating parameter sets described in *Table 9*) equal volumes of headspace of the *Class 1 standard solution*, *Class 1 system suitability solution*, *Class 2 mixture A standard solution*, *Class 2 mixture B standard solution*, and *Sample solution* into the chromatograph, record the chromatograms, and measure the responses for the peaks of interest.

System suitability requirements (see *Figure 4*): The S/N ratio for benzene in the *Class 1 standard solution* is NLT 5. The S/N ratio of each peak in the *Class 1 system suitability solution* is NLT 3, and the resolution between **▲methylisobutylketone▲** (IRA 1-Nov-2019) and *cis*-dichloroethene in the *Class 2 mixture A standard solution* is NLT 1.0.

Acceptance criteria: If the response(s) in the *Sample solution* of the peak(s) identified in *Procedure A* is are greater than or equal to corresponding peak(s) in either the *Class 1 standard solution*, or either *Class 2 mixture A standard solution* or *Class 2 mixture B standard solution*, proceed to *Procedure C* to quantify the peak(s); otherwise the article meets the requirements of this test.

## 8.3 Screening of Water-Insoluble Articles

## STOCK SOLUTIONS

[NOTE—Dimethyl sulfoxide may be substituted as an alternative solvent to dimethylformamide. When transferring solutions, place the tip of the pipet just below the surface of the liquid and mix.]

Class 1 standard stock solution: Transfer 1.0 mL of USP Residual Solvents Mixture—Class 1 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 (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 2 mixture A standard stock solution: Transfer 1.0 mL of USP Residual Solvents Class 2—Mixture A RS to a 100-mL volumetric flask containing about 80 mL of dimethylformamide, dilute with dimethylformamide to volume, and mix.

Class 2 mixture B standard stock solution: 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.

Sample 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.

## SYSTEM SUITABILITY SOLUTION

Class 1 system suitability solution: Mix 5 mL of *Sample stock solution* with 0.5 mL of the intermediate dilution reserved from *Class 1 standard stock solution*. Transfer 1 mL of this solution to an appropriate headspace vial containing 5 mL of water. Apply the stopper, cap, and mix.

## STANDARD SOLUTIONS

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 mixture A standard solution: Transfer 1.0 mL of *Class 2 mixture A standard stock solution* 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 mixture B standard stock solution* to an appropriate headspace vial containing 5.0 mL of water, apply the stopper, cap, and mix.

## SAMPLE SOLUTION

Sample solution: Transfer 1.0 mL of *Sample stock solution* to an appropriate headspace vial containing 5.0 mL of water, apply the stopper, cap, and mix.

## PROCEDURE A

Analysis: Proceed as directed for *Procedure A* in *8.2 Screening of Water-Soluble Articles* with a split ratio of 1:3. [NOTE—The split ratio can be modified in order to optimize sensitivity.] Separately inject (using one of the headspace operating parameter sets described in *Table 9* with a recommended vial pressure of 10 psi) equal volumes of headspace of the *Class 1 standard solution*, *Class 2 mixture A standard solution*, *Class 2 mixture B standard solution*, and *Sample solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks.

System suitability requirements (see *Figure 4*): The S/N ratio for 1,1,1-trichloroethane in the *Class 1 standard solution* is NLT 5. The S/N ratio of each peak in the *Class 1 system suitability solution* is NLT 3; and the resolution between acetonitrile and methylene chloride in the *Class 2 mixture A standard solution* is NLT 1.0.

Acceptance criteria: If a response of any peak, other than the peak for 1,1,1-TCE in the *Sample solution* is greater than or equal to a corresponding peak in either the *Class 1 standard solution*, or either *Class 2 mixture A standard solution* or *Class 2 mixture B standard solution*, 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

Analysis: Proceed as directed for *Procedure B* in *8.2 Screening of Water-Soluble Articles* with a split ratio of 1:3. Separately inject (using one of the headspace operating parameter sets described in *Table 9* with a recommended vial pressure of 10 psi) equal volumes of headspace of the *Class 1 standard solution*, *Class 2 mixture A standard solution*, *Class 2 mixture B standard solution*, *Sample solution*, and *Class 1 system suitability solution* into the chromatograph, record the chromatograms, and measure the responses for the peaks of interest.

System suitability requirements (see *Figure 4*): The S/N ratio for benzene in the *Class 1 standard solution* is NLT 5. The S/N ratio of each peak in the *Class 1 system suitability solution* is NLT 3; and the resolution between ▲methylisobutylketone▲ (IRA 1-Nov-2019) and *cis*-dichloroethene in the *Class 2 mixture A standard solution* is NLT 1.0.

Acceptance criteria: If the peak response(s) in the *Sample solution* of the peak(s) identified in *Procedure A* is/are greater than or equal to corresponding peak(s) in either the *Class 1 standard solution*, or either *Class 2 mixture A standard solution* or *Class 2 mixture B standard solution*, proceed to *Procedure C* to quantify the peak(s); otherwise the article meets the requirements of this test.

## 8.4 Limit Tests When Solvents LTBP Are Known

### SOLUTIONS

Prepare the standard solution and the *Sample solution* as directed in *8.2 Screening of Water-Soluble Articles* or *8.3 Screening of Water-Insoluble Articles* according to the procedure chosen based on the sample solubility. Use USP Reference Standards for those solvents LTBP to prepare the standard solution.

When solvents LTBP are known, only the standards of those solvents LTBP are needed, and determination may be done using a limit test or a quantitative test. Only quantitative tests can be used for *Option 2*.

System suitability solution: Prepare the *System suitability solution* according to the solubility of the sample for screening for water-soluble or water-insoluble articles at the concentration of the standard solutions there. Use only those solvents LTBP.

### PROCEDURE A

Analysis (limit test): Separately inject (using one of the headspace operating parameter sets described in *Table 9*) equal volumes of headspace of the *System suitability solution*, *Standard solution*, and *Sample solution* into the chromatograph, record the chromatograms, and measure the responses for the peaks of interest.

System suitability requirements (see *Figure 4*): The S/N ratio for 1,1,1-trichloroethane, if present, is NLT 5. The S/N ratio is NLT 3 for any other solvent. If there is more than one solvent LTBP, the resolution between a peak of interest and any adjacent peak is NLT 1.0.

Acceptance criteria: If the peak response of every peak of interest in the *Sample solution* is smaller than the corresponding peak in the *Standard solution*, the article meets the requirements of this test.

## PROCEDURE B

Analysis (limit test): Separately inject (following one of the headspace operating parameter sets described in *Table 9*) equal volumes of headspace of the *Standard solution* and *Sample solution* into the chromatograph, record the chromatograms, and measure the responses for the peaks of interest.

System suitability requirements (see *Figure 4*): The S/N ratio for benzene, if present, is NLT 5. The S/N ratio is NLT 3 for any other solvent. If there is more than one solvent LTBP, the resolution between a peak of interest and any other peak is NLT 1.0.

Acceptance criteria: If the peak response of every peak of interest in the *Sample solution* is smaller than the corresponding peak in the *Standard solution*, the article meets the requirements of this test.

## 8.5 Quantitative Tests—Procedure C

## QUANTIFICATION FOR WATER-SOLUBLE ARTICLES

(Use the requirement for *General* or *Targeted test*, as applicable.)

Sample stock solution: Prepare a *Sample stock solution* as directed in *8.2 Screening of Water-Soluble Articles, Stock Solutions*. ▲ (IRA 1-Nov-2019)

Standard stock solution: [NOTE—Prepare a separate *Standard stock solution* for each solvent LTBP or potentially LTBP, or identified and verified by *Procedure A* and *Procedure 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*.] Transfer an accurately measured volume of each individual USP Reference Standard corresponding to each residual solvent peak LTBP or identified and verified by *Procedure A* and *Procedure B* to a suitable container, and dilute quantitatively and stepwise, if necessary, with water to obtain a solution with a final concentration of 1/20 of the value stated in *Table 2* or *Table 3* under *Concentration Limit*.

Standard solution: Transfer 1.0 mL of *Standard stock solution* to an appropriate headspace vial, add 5.0 mL of water, apply the stopper, cap, and mix.

Sample solution: Prepare as directed in *8.2 Screening of Water-Soluble Articles, Sample Solution*.

Spiked sample solution: [NOTE—Prepare a separate *Spiked sample solution* for each peak LTBP or potentially LTBP or identified and verified by *Procedure A* and *Procedure B*.] Transfer 5.0 mL of each *Sample stock solution* to an appropriate headspace vial, add 1.0 mL of the *Standard stock solution*, apply the stopper, cap, and mix. The use of a vial containing the sample spiked with multiple standards is permitted, provided that the procedure is validated accordingly.

Analysis: Proceed as directed for *Procedure A*. [NOTE—If the performance of *Procedure B* is better than that shown by *Procedure A*, then *Procedure B* may be used for quantification.] Separately inject (using one of the headspace operating parameter sets described in *Table 9* with a recommended vial pressure of 10 psi) equal volumes of headspace of the *Standard solution*, *Sample solution*, and *Spiked sample solution* into the chromatograph, record the chromatograms, and measure the responses for the peaks of interest.

System suitability requirements for Procedure A (see *Figure 4*):

General: Same as in *8.2 Screening of Water-Soluble Articles, Procedure A*.

Targeted test: The S/N ratio is NLT 10 for any solvent except NLT 5 for 1,1,1-trichloroethane and NLT 3 for any other Class 1 solvent, if present. If there is more than one solvent LTBP, the resolution between a peak of interest and any adjacent peak is NLT 1.0.

System suitability requirements for Procedure B (see *Figure 4*):

General: Same as in *8.2 Screening of Water-Soluble Articles, Procedure B*.

Targeted test: The S/N ratio is NLT 10 for any solvent except NLT 5 for benzene and NLT 3 for any other Class 1 solvent, if present. If there is more than one solvent LTBP, the resolution between a peak of interest and any adjacent peak is NLT 1.0.

Calculate the amount, in ppm, of each residual solvent found in the article under test:

$$\text{Result} = 5(CW)[r_J(r_{ST} - r_U)]$$

- C* = concentration of the appropriate USP Reference Standard in the *Standard stock solution* (µg/mL)  
*W* = weight of the article under test taken to prepare the *Sample stock solution* (g)  
*r<sub>U</sub>* = peak responses of each residual solvent obtained from the *Sample solution*  
*r<sub>ST</sub>* = peak responses of each residual solvent obtained from the *Spiked sample solution*

## QUANTIFICATION FOR WATER-INSOLUBLE ARTICLES

(Use the requirement for *General* or *Targeted test* as applicable.)

Sample stock solution: Prepare a *Sample stock solution* as directed in *8.3 Screening of Water-Insoluble Articles, Stock Solutions*. Only the Reference Standard for those solvents identified by *Procedure A* or *Procedure B* or LTBP need to be used.

Standard stock solution: [NOTE—Prepare a separate *Standard stock solution* for each solvent LTBP or potentially LTBP, or identified and verified by *Procedure A* and *Procedure 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*.] Transfer an accurately measured volume of each individual USP Reference Standard corresponding to each residual solvent peak LTBP or identified and verified by *Procedure A* and *Procedure B* to a suitable container, and dilute quantitatively and stepwise, if necessary, with water to obtain a solution with a final concentration of 1/20 of the value stated in *Table 2* or *Table 3* under *Concentration Limit*.

Standard solution: Transfer 1.0 mL of *Standard stock solution* to an appropriate headspace vial, containing 5.0 mL of water, apply the stopper, cap, and mix.

Sample solution: Transfer 1.0 mL of *Sample stock solution* to an appropriate headspace vial, containing 5.0 mL of water, apply the stopper, cap, and mix.

Spiked sample solution: [NOTE—Prepare a separate *Spiked sample solution* for each peak LTBP or potentially LTBP, or identified and verified by *Procedure A* and *Procedure B*] Transfer 1.0 mL of each *Sample stock solution* to an appropriate headspace vial, add 1.0 mL of *Standard stock solution* and 4.0 mL of water, and apply the stopper, cap, and mix. The use of a vial containing the sample spiked with multiple standards is permitted, provided that the procedure is validated accordingly.

Analysis: Proceed as directed for *Procedure A* [NOTE—If the performance of *Procedure B* is better than that shown by *Procedure A*, then *Procedure B* may be used for quantification.] Separately inject (using one of the headspace operating parameter sets described in *Table 9* with a recommended vial pressure of 10 psi) equal volumes of headspace of the *Standard solution*, *Sample solution*, and *Spiked sample solution* into the chromatograph, record the chromatograms, and measure the responses for the peaks of interest. If Class 1 solvents are LTBP, also inject the *Class 1 system suitability solution*.

System suitability requirements for Procedure A (see *Figure 4*):

General: Same as in *8.3 Screening of Water-Insoluble Articles, Procedure A*.

Targeted test: The S/N ratio is NLT 10 for any solvent except NLT 5 for 1,1,1-trichloroethane and NLT 3 for any other Class 1 solvent, if present. If there is more than one solvent LTBP, the resolution between a peak of interest and any adjacent peak is NLT 1.0.

System suitability requirements for Procedure B (see *Figure 4*):

General: Same as in *8.3 Screening of Water-Insoluble Articles, Procedure B*.

Targeted test: The S/N ratio is NLT 10 for any solvent except NLT 5 for benzene and NLT 3 for any other Class 1 solvent, if present. If there is more than one solvent LTBP, the resolution between a peak of interest and any adjacent peak is NLT 1.0.

Calculate the amount, in ppm, of each residual solvent found in the article under test:

$$\text{Result} = 10(CW)[r_U(r_{ST} - r_U)]$$

$C$  = concentration of the appropriate USP Reference Standard in the *Standard stock solution* ( $\mu\text{g/mL}$ )

$W$  = weight of the article under test taken to prepare the *Sample stock solution* (g)

$r_U$  = peak responses of each residual solvent obtained from the *Sample solution*

$r_{ST}$  = peak responses of each residual solvent obtained from the *Spiked sample solution*

## 9. ANALYTICAL PROCEDURES FOR CLASS 3 RESIDUAL SOLVENTS

If only Class 3 solvents are present, and the monograph for the article under test contains an LOD procedure specifying an upper limit of NMT 0.5% (per *Option 1* in this chapter), then the level of residual solvent can be determined as directed in *Loss on Drying* (731). If Class 3 solvents are present with other solvents, e.g., Class 1 or Class 2 solvents, or if there is no LOD procedure in the monograph for the article under test, or if the limit for Class 3 solvent(s) in an individual monograph is greater than 50 mg/day (corresponding to 5000 ppm or 0.5% under *Option 1*), then the Class 3 residual solvent or solvents present in the article under test should be identified and quantified. In that case, the procedures described in this chapter, with appropriate adjustments, are to be applied wherever possible and USP Reference Standards, where available, should be used in these procedures. Such procedures should be properly validated as described in (1467). If Class 1 or Class 2 solvents are present and LOD is less than 0.5%, then identification of Class 3 solvents is not required and only Class 1 and Class 2 solvents should be identified and quantified. See *Figure 5*.

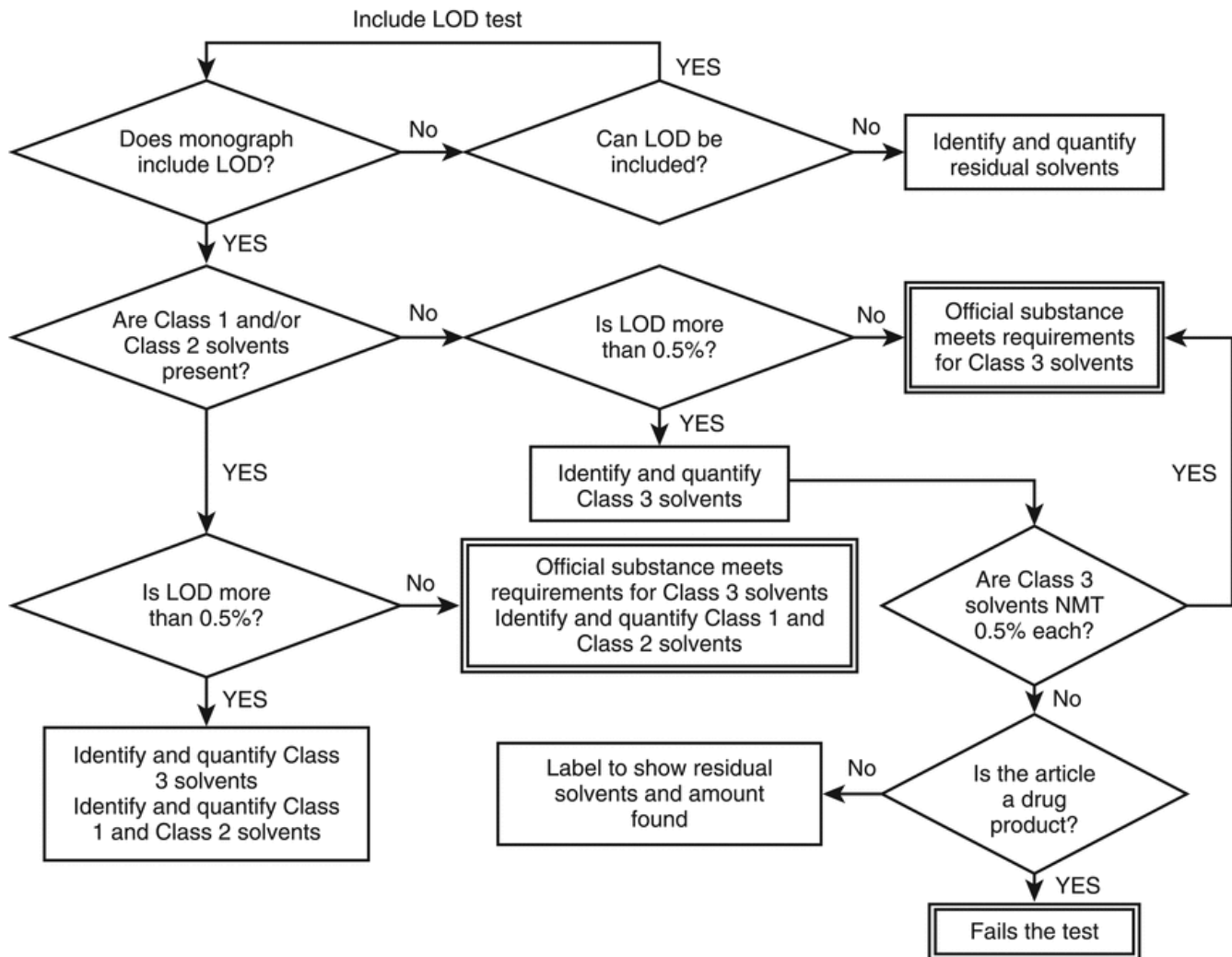


Figure 5. Decision tree for the control of Class 3 residual solvents. LOD: Loss on drying.

## GLOSSARY

**Genotoxic carcinogens:** Carcinogens that produce cancer by affecting genes or chromosomes.

**Likely to be present (LTBP):** Those solvents that are 1) used or produced in the final manufacturing step; 2) used or produced in earlier manufacturing steps but they are not consistently removed by a validated process; 3) the solvents properly declared by a validated supplier of a drug substance, excipient, or dietary ingredient.

**Lowest-observed-effect level (LOEL):** The lowest dose of a substance in a study or group of studies that produces biologically significant increases in frequency or severity of any effects in exposed humans or animals.

**Modifying factor:** A factor determined by professional judgment of a toxicologist and applied to bioassay data so that the data can be safely related to humans.

**Neurotoxicity:** The ability of a substance to cause adverse effects on the nervous system.

**No-observed-effect level (NOEL):** The highest dose of a substance at which there are no biologically significant increases in frequency or severity of any effects in exposed humans or animals.

**Permitted daily exposure (PDE):** The maximum acceptable intake per day of a residual solvent in pharmaceutical products or dietary supplements.

**Reversible toxicity:** The occurrence of harmful effects that are caused by a substance and then disappear after the exposure to the substance ends.

**Strongly suspected human carcinogen:** A substance for which there is no epidemiological evidence of carcinogenesis but for which there are positive genotoxicity data and clear evidence of carcinogenesis in rodents.

**Teratogenicity:** The occurrence of structural malformations in a developing fetus when a substance is administered during pregnancy.



Change to read:

APPENDICES

Appendix 1: Residual Solvents Included in this General Chapter

See Table A-1 for a list of residual solvents included in this chapter.

Table A-1. List of Residual Solvents Included in this General Chapter

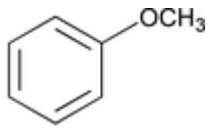

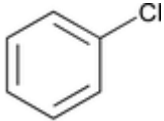
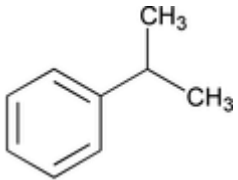
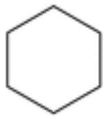
Solvent	Other Names	Structure	Class
Acetic acid	Ethanoic acid	$\text{CH}_3\text{COOH}$	Class 3
Acetone	2-Propanone; Propan-2-one	$\text{CH}_3\text{COCH}_3$	Class 3
Acetonitrile	AcN	$\text{CH}_3\text{CN}$	Class 2
Anisole	Methoxybenzene		Class 3
Benzene	Benzol		Class 1
1-Butanol	<i>n</i> -Butyl alcohol; Butan-1-ol	$\text{CH}_3(\text{CH}_2)_3\text{OH}$	Class 3
2-Butanol	<i>sec</i> -Butyl alcohol; Butan-2-ol	$\text{CH}_3\text{CH}_2\text{CH}(\text{OH})\text{CH}_3$	Class 3
Butyl acetate	Acetic acid butyl ester	$\text{CH}_3\text{COO}(\text{CH}_2)_3\text{CH}_3$	Class 3
<i>tert</i> -Butylmethyl ether	2-Methoxy-2-methylpropane	$(\text{CH}_3)_3\text{COCH}_3$	Class 3
Carbon tetrachloride	Tetrachloromethane	$\text{CCl}_4$	Class 1
Chlorobenzene			Class 2
Chloroform	Trichloromethane	$\text{CHCl}_3$	Class 2
Cumene	Isopropylbenzene; (1-Methylethyl)benzene		Class 2
Cyclohexane	Hexamethylene		Class 2
1,2-Dichloroethane	<i>sym</i> -Dichloroethane; Ethylene dichloride; Ethylene chloride	$\text{CH}_2\text{ClCH}_2\text{Cl}$	Class 1
1,1-Dichloroethene	1,1-Dichloroethylene; Vinylidene chloride	$\text{H}_2\text{C}=\text{CCl}_2$	Class 1
1,2-Dichloroethene	1,2-Dichloroethylene; Acetylene dichloride; DCE	$\text{ClHC}=\text{CHCl}$	Class 2

Table A-1. List of Residual Solvents Included in this General Chapter (continued)

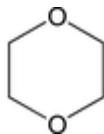
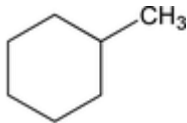
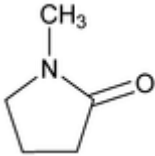
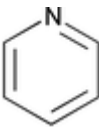
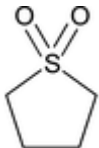

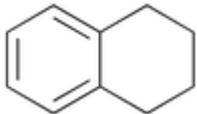
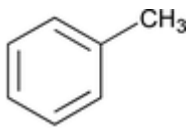
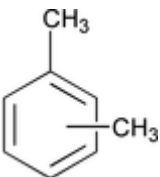
Solvent	Other Names	Structure	Class
1,2-Dimethoxyethane	Ethyleneglycol dimethyl ether; Monoglyme; Dimethyl cellosolve	$\text{H}_3\text{COCH}_2\text{CH}_2\text{OCH}_3$	Class 2
<i>N,N</i> -Dimethylacetamide	DMA	$\text{CH}_3\text{CON}(\text{CH}_3)_2$	Class 2
<i>N,N</i> -Dimethylformamide	Dimethylformamide	$\text{HCON}(\text{CH}_3)_2$	Class 2
Dimethyl sulfoxide	Methylsulfinylmethane; Methyl sulfoxide; Dimethyl sulfoxide	$(\text{CH}_3)_2\text{SO}$	Class 3
1,4-Dioxane	<i>p</i> -Dioxane; [1,4]Dioxane		Class 2
Ethanol	Ethyl alcohol	$\text{CH}_3\text{CH}_2\text{OH}$	Class 3
2-Ethoxyethanol	Cellosolve	$\text{CH}_3\text{CH}_2\text{OCH}_2\text{CH}_2\text{OH}$	Class 2
Ethyl acetate	Acetic acid ethyl ester	$\text{CH}_3\text{COOCH}_2\text{CH}_3$	Class 3
Ethylene glycol	1,2-Dihydroxyethane; 1,2-Ethanediol	$\text{HOCH}_2\text{CH}_2\text{OH}$	Class 2
Ethyl ether	Diethyl ether; Ethoxyethane; 1,1'-Oxybisethane	$\text{CH}_3\text{CH}_2\text{OCH}_2\text{CH}_3$	Class 3
Ethyl formate	Formic acid ethyl ester	$\text{HCOOCH}_2\text{CH}_3$	Class 3
Formamide	Methanamide	$\text{HCONH}_2$	Class 2
Formic acid		$\text{HCOOH}$	Class 3
Heptane	<i>n</i> -Heptane	$\text{CH}_3(\text{CH}_2)_5\text{CH}_3$	Class 3
Hexane	<i>n</i> -Hexane	$\text{CH}_3(\text{CH}_2)_4\text{CH}_3$	Class 2
Isobutyl acetate	Acetic acid isobutyl ester	$\text{CH}_3\text{COOCH}_2\text{CH}(\text{CH}_3)_2$	Class 3
Isopropyl acetate	Acetic acid isopropyl ester	$\text{CH}_3\text{COOCH}(\text{CH}_3)_2$	Class 3
Methanol	Methyl alcohol	$\text{CH}_3\text{OH}$	Class 2
2-Methoxyethanol	Methyl cellosolve	$\text{CH}_3\text{OCH}_2\text{CH}_2\text{OH}$	Class 2
Methyl acetate	Acetic acid methyl ester	$\text{CH}_3\text{COOCH}_3$	Class 3
3-Methyl-1-butanol	Isoamyl alcohol; Isopentyl alcohol; 3-Methylbutan-1-ol	$(\text{CH}_3)_2\text{CHCH}_2\text{CH}_2\text{OH}$	Class 3
Methylbutylketone	2-Hexanone; Hexan-2-one	$\text{CH}_3(\text{CH}_2)_3\text{COCH}_3$	Class 2
Methylcyclohexane	Cyclohexylmethane		Class 2
Methylene chloride	Dichloromethane; MC	$\text{CH}_2\text{Cl}_2$	Class 2
Methylethylketone	2-Butanone; MEK; Butan-2-one	$\text{CH}_3\text{CH}_2\text{COCH}_3$	Class 3
▲Methylisobutylketone▲ (Official 1-Dec-2020)	4-Methylpentan-2-one; 4-Methyl-2-pentanone; MIBK	$\text{CH}_3\text{COCH}_2\text{CH}(\text{CH}_3)_2$	Class ▲2▲ (Official 1-Dec-2020)
2-Methyl-1-propanol	Isobutyl alcohol; 2-Methylpropan-1-ol	$(\text{CH}_3)_2\text{CHCH}_2\text{OH}$	Class 3

Table A-1. List of Residual Solvents Included in this General Chapter (continued)

Solvent	Other Names	Structure	Class
<i>N</i> -Methylpyrrolidone	1-Methylpyrrolidin-2-one; 1-Methyl-2-pyrrolidinone		Class 2
Nitromethane		CH <sub>3</sub> NO <sub>2</sub>	Class 2
Pentane	<i>n</i> -Pentane	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>3</sub> CH <sub>3</sub>	Class 3
1-Pentanol	Amyl alcohol; Pentan-1-ol; Pentyl alcohol	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>3</sub> CH <sub>2</sub> OH	Class 3
1-Propanol	Propan-1-ol; Propyl alcohol	CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> OH	Class 3
2-Propanol	Propan-2-ol; Isopropyl alcohol	(CH <sub>3</sub> ) <sub>2</sub> CHOH	Class 3
Propyl acetate	Acetic acid propyl ester	CH <sub>3</sub> COOCH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	Class 3
Pyridine			Class 2
Sulfolane	Tetrahydrothiophene 1,1-dioxide		Class 2
Tetrahydrofuran	Tetramethylene oxide; Oxacyclopentane		Class 2
Tetralin	1,2,3,4-Tetrahydronaphthalene		Class 2
Toluene	Methylbenzene		Class 2
1,1,1-Trichloroethane	Methylchloroform; 1,1,1-TCE	CH <sub>2</sub> CCl <sub>3</sub>	Class 1
Trichloroethylene	1,1,2-Trichloroethene	HCl=CCl <sub>2</sub>	Class 2
<sup>▲</sup> Triethylamine	<i>N,N</i> -Diethylethanamine	(CH <sub>3</sub> CH <sub>2</sub> ) <sub>3</sub> N	Class 3 <sup>▲</sup> (Official 1-Dec-2020)
Xylene <sup>a</sup>	Dimethylbenzene; Xylo <sup>l</sup>		Class 2

<sup>a</sup> Usually 60% *m*-xylene, 14% *p*-xylene, and 9% *o*-xylene with 17% ethyl benzene.

## Appendix 2: Additional Background

## ENVIRONMENTAL REGULATION OF ORGANIC VOLATILE SOLVENTS

Several of the residual solvents frequently used in the production of pharmaceuticals are listed as toxic chemicals in *Environmental Health Criteria* (EHC) monographs and in the *Integrated Risk Information System* (IRIS) and other similar reference material. The approach to risk assessment described therein relates primarily to long-term or lifetime exposure of the general population via the ambient environment (i.e., inhaled air, food, drinking water, and other sources). The objectives of such groups as the International Programme on Chemical Safety (IPCS), the U.S. Environmental Protection Agency (EPA), and the U.S. Food and Drug Administration (FDA) include the determination of acceptable exposure levels. The goal is maintenance of environmental integrity and protection of human health against the possible deleterious effects of chemicals resulting from long-term environmental exposure. The procedures involved in the estimation of maximum safe exposure limits are usually based on long-term studies. When long-term study data are unavailable, shorter-term study data can be used with modification of the approach, such as use of larger safety factors.

## RESIDUAL SOLVENTS IN PHARMACEUTICALS

Exposure limits in this chapter were established by referring to methodologies and toxicity data described in EHC and IRIS monographs. However, the following specific assumptions about residual solvents to be used in the synthesis and formulation of pharmaceutical products should be taken into account in establishing exposure limits.

1. Patients (not the general population) use pharmaceuticals to treat their diseases or for prophylaxis to prevent infection or disease.
2. The assumption of lifetime patient exposure is not necessary for most pharmaceutical products but may be appropriate as a working hypothesis to reduce risk to human health.
3. Residual solvents are unavoidable components in pharmaceutical production and will often be a part of pharmaceutical drug products.
4. Residual solvents should not exceed recommended levels except in exceptional circumstances.
5. Data from toxicological studies that are used to determine acceptable levels for residual solvents should have been generated using appropriate protocols such as those described by the Organization for Economic Cooperation and Development (OECD), the EPA, and the FDA *Redbook* or derived from alternative sources also considered to be adequate to support PDE limit setting.

## Appendix 3: Procedures for Establishing Exposure Limits

The Gaylor–Kodell method of risk assessment (Gaylor, DW, Kodell, FL. Linear interpolation algorithm for low dose risk assessment of toxic substances. *J Environ Pathol, Toxicol*, 1980;4:305–312) is appropriate for Class 1 carcinogenic solvents. Only in cases where reliable carcinogenicity data are available should extrapolation by the use of mathematical models be applied to setting exposure limits. Exposure limits for Class 1 residual solvents could be determined with the use of a large safety factor (i.e., 10,000–100,000) with respect to the no-observed-effect level (NOEL). Detection and quantification of these residual solvents should be performed using state-of-the-art analytical techniques.

Acceptable exposure levels in this chapter for Class 2 residual solvents were established by calculation of PDE values according to the procedures for setting exposure limits in pharmaceuticals (page 5748 of *Pharmacoepial Forum* [Nov.–Dec. 1989]), and the method adopted by IPCS for *Assessing Human Health Risks of Chemicals* (*Environmental Health Criteria 170*, WHO, 1994), detailed calculations are published in *Pharmeuropa*, Vol. 9, No. 1, Supplement, April 1997. These procedures are similar to those used by the U.S. EPA (IRIS) and the U.S. FDA (*Redbook*) and others. The method is outlined here to give a better understanding of the origin of the PDE values. It is not necessary to perform these calculations in order to use the PDE values presented in *Table 3* of this document.

PDE is derived from the NOEL, or the lowest-observed-effect level (LOEL), in the most relevant animal study as follows:

$$PDE = (\text{NOEL} \times \text{Weight Adjustment}) / (F1 \times F2 \times F3 \times F4 \times F5)$$

The PDE is derived preferably from a NOEL. If no NOEL is obtained, the LOEL may be used. Modifying factors proposed here, for relating the data to humans, are the same kind of “uncertainty factors” used in *Environmental Health Criteria* (*Environmental Health Criteria 170*, WHO, 1994) and “modifying factors” or “safety factors” used in *Pharmacoepial Forum*. The assumption of 100% systemic exposure is used in all calculations regardless of the route of administration.

The modifying factors are as follows:

*F1* = A factor to account for extrapolation between species.

*F1* = 5 for extrapolation from rats to humans

*F1* = 12 for extrapolation from mice to humans

*F1* = 2 for extrapolation from dogs to humans

*F1* = 2.5 for extrapolation from rabbits to humans

*F1* = 3 for extrapolation from monkeys to humans

*F1* = 10 for extrapolation from other animals to humans

*F1* takes into account the comparative surface area to body weight ratios for the species concerned and for humans. Surface area (*S*) is calculated as:

$$S = kM^{0.67}$$

$k$  = a constant that has been taken to be 10  
 $M$  = body weight

The body weights used in the equation are those shown below in *Table A-2*:

$F_2$  = A factor of 10 to account for variability between individuals.

A factor of 10 is generally given for all organic solvents, and 10 is used consistently in this chapter.

$F_3$  = A variable factor to account for toxicity studies of short-term exposure

$F_3 = 1$  for studies that last at least one half lifetime (1 year for rodents or rabbits; 7 years for cats, dogs, and monkeys)

$F_3 = 1$  for reproductive studies in which the whole period of organogenesis is covered

$F_3 = 2$  for a 6-month study in rodents, or a 3.5-year study in non-rodents

$F_3 = 5$  for a 3-month study in rodents, or a 2-year study in non-rodents

$F_3 = 10$  for studies of a shorter duration

In all cases, the higher factor has been used for study durations between the time points (e.g., a factor of 2 for a 9-month rodent study).

$F_4$  = A factor that may be applied in cases of severe toxicity, e.g., nongenotoxic carcinogenicity, neurotoxicity, or teratogenicity. In studies of reproductive toxicity, the following factors are used:

$F_4 = 1$  for fetal toxicity associated with maternal toxicity

$F_4 = 5$  for fetal toxicity without maternal toxicity

$F_4 = 5$  for a teratogenic effect with maternal toxicity

$F_4 = 10$  for a teratogenic effect without maternal toxicity

$F_5$  = A variable factor that may be applied if the no-effect level was not established.

When only a LOEL is available, a factor of up to 10 can be used, depending on the severity of the toxicity. The weight adjustment assumes an arbitrary adult human body weight for either sex of 50 kg. This relatively low weight provides an additional safety factor against the standard weights of 60 or 70 kg that are often used in this type of calculation. It is recognized that some adult patients weigh less than 50 kg; these patients are considered to be accommodated by the built-in safety factors used to determine a PDE. If the solvent was present in a formulation specifically intended for pediatric use, an adjustment for a lower body weight would be appropriate.

As an example of the application of this equation, consider a toxicity study of acetonitrile in mice that is summarized in *Pharmeuropa*, 1997;9(1): S24. The NOEL is calculated to be 50.7 mg kg<sup>-1</sup> day<sup>-1</sup>. The PDE for acetonitrile in this study is calculated as follows:

$$\text{PDE} = (50.7 \text{ mg kg}^{-1} \text{ day}^{-1} \times 50 \text{ kg}) / (12 \times 10 \times 5 \times 1 \times 1) = 4.22 \text{ mg day}^{-1}$$

In this example,

$F_1 = 12$  to account for the extrapolation from mice to humans

$F_2 = 10$  to account for differences between individual humans

$F_3 = 5$  because the duration of the study was only 13 weeks

$F_4 = 1$  because no severe toxicity was encountered

$F_5 = 1$  because the no-effect level was determined

Table A-2. Values Used in the Calculations in This Chapter

Rat body weight	425 g
Pregnant rat body weight	330 g
Mouse body weight	28 g
Pregnant mouse body weight	30 g
Guinea-pig body weight	500 g
Rhesus monkey body weight	2.5 kg
Rabbit body weight (pregnant or not)	4 kg
Beagle dog body weight	11.5 kg
Rat respiratory volume	290 L/day
Mouse respiratory volume	43 L/day
Rabbit respiratory volume	1440 L/day
Guinea-pig respiratory volume	430 L/day
Human respiratory volume	28,800 L/day
Dog respiratory volume	9000 L/day
Monkey respiratory volume	1150 L/day
Mouse water consumption	5 mL/day

Table A-2. Values Used in the Calculations in This Chapter (*continued*)

Rat water consumption	30 mL/day
Rat food consumption	30 g/day

The equation for an ideal gas,  $PV = nRT$ , is used to convert concentrations of gases used in inhalation studies from units of ppm to units of mg/L or mg/m<sup>3</sup>. Consider as an example the rat reproductive toxicity study by inhalation of carbon tetrachloride (molecular weight, 153.84) summarized in *Pharmeuropa*, 1997:9(1):S9.

$$\frac{n}{V} = \frac{P}{RT} = \frac{300 \times 10^{-6} \text{ atm} \times 153,840 \text{ mg mol}^{-1}}{0.082 \text{ L at mK}^{-1} \text{ mol}^{-1} \times 298 \text{ K}} = \frac{46.15 \text{ mg}}{24.45 \text{ L}} = 1.89 \text{ mg/L}$$

The relationship 1000 L = 1 m<sup>3</sup> is used to convert to mg/m<sup>3</sup>.

*Change to read:*

USP Reference Standards <11>

USP 1-Butanol RS  
 USP 2-Butanol RS  
 USP 2-Methyl-1-Propanol RS  
 USP 3-Methyl-1-butanol RS  
 USP 1-Pentanol RS  
 USP 1-Propanol RS  
 USP 2-Propanol RS  
 USP Acetone RS  
 USP Alcohol Determination—Alcohol RS  
 USP Anisole RS  
 USP Butyl Acetate RS  
 USP *tert*-Butylmethyl Ether RS  
 USP Dimethyl Sulfoxide RS  
 USP Ethyl Acetate RS  
 USP Ethyl Formate RS  
 USP Formic Acid RS  
 USP Glacial Acetic Acid RS  
 USP Heptane RS  
 USP Isobutyl Acetate RS  
 USP Isopropyl Acetate RS  
 USP Methyl Acetate RS  
 USP Methyl Ethyl Ketone RS  
 ▲▲ (IRA 1-Nov-2019)  
 USP Pentane RS  
 USP Propyl Acetate RS  
 USP Residual Solvents Mixture—Class 1 RS  
 USP Residual Solvent Class 1—Benzene RS  
 USP Residual Solvent Class 1—Carbon Tetrachloride RS  
 USP Residual Solvent Class 1—1,2-Dichloroethane RS  
 USP Residual Solvent Class 1—1,1-Dichloroethene RS  
 USP Residual Solvent Class 1—1,1,1-Trichloroethane RS  
 USP Residual Solvents Class 2—Mixture A RS  
 USP Residual Solvents Class 2—Mixture B RS  
 USP Residual Solvent Class 2—Mixture C RS  
 USP Residual Solvent Class 2—Acetonitrile RS  
 USP Residual Solvent Class 2—Chlorobenzene RS  
 USP Residual Solvent Class 2—Chloroform RS  
 USP Residual Solvent Class 2—Cumene RS  
 USP Residual Solvent Class 2—Cyclohexane RS  
 USP Residual Solvent Class 2—1,2-Dichloroethene RS  
 USP Residual Solvent Class 2—1,2-Dimethoxyethane RS  
 USP Residual Solvent Class 2—*N,N*-Dimethylacetamide RS  
 USP Residual Solvent Class 2—*N,N*-Dimethylformamide RS  
 USP Residual Solvent Class 2—1,4-Dioxane RS  
 USP Residual Solvent Class 2—2-Ethoxyethanol RS  
 USP Residual Solvent Class 2—Ethylene Glycol RS  
 USP Residual Solvent Class 2—Hexane RS  
 USP Residual Solvent Class 2—Methanol RS  
 USP Residual Solvent Class 2—2-Methoxyethanol RS  
 USP Residual Solvent Class 2—Methylbutylketone RS  
 USP Residual Solvent Class 2—Methylcyclohexane RS  
 USP Residual Solvent Class 2—Methylene Chloride RS

▲  
USP Residual Solvent Class 2—Methylisobutylketone RS

▲ (IPA 1-Nov-2019)

USP Residual Solvent Class 2—*N*-Methylpyrrolidone RS

USP Residual Solvent Class 2—Nitromethane RS

USP Residual Solvent Class 2—Pyridine RS

USP Residual Solvent Class 2—Tetrahydrofuran RS

USP Residual Solvent Class 2—Tetralin RS

USP Residual Solvent Class 2—Toluene RS

USP Residual Solvent Class 2—Trichloroethylene RS

USP Residual Solvent Class 2—Xylenes RS

▲

USP Triethylamine RS

▲ (IPA 1-Nov-2019)