

**USP <467>**

The United States Pharmacopeia (USP) general chapter <467> *Residual Solvents* is a widely used compendial method intended for identifying and quantifying residual solvents in drug substances, drug products, and excipients. In an attempt to better mirror the International Conference on Harmonization (ICH) guidelines, the USP is proposing a more comprehensive methodology in residual solvent testing—the current USP30/NF25. The ICH publishes a guideline (Q3C) listing the acceptable amounts of solvent residues that can be present. In the ICH guideline, residual solvents are summarized by class, according to their toxicity. Class 1 compounds are carcinogenic compounds that pose a risk to both the consumer and the environment. The use of these solvents is to be avoided, but if they are used, they must be tightly controlled. Class 2 compounds are nongenotoxic animal carcinogens, and concentrations of these compounds should be limited. Chromatographic analysis is needed for both the Class 1 and Class 2 residual solvents.

Initially set to become effective July 1, 2007, the implementation of the current version of USP <467>: *Residual Solvents* has been delayed until July 1, 2008. Until that time, the *Other Analytical Procedures* section of the previous version will be retained.

also available

For a list of OVI retention times, see page 721.

**USP <467> Singles**

Volume is 1mL/ampul.

Compound	Solvent	Conc.	cat.# (ea.)
acetonitrile	DMSO	2.05mg/mL	36281
benzene	DMSO	10mg/mL	36282
carbon tetrachloride	DMSO	20mg/mL	36283
chlorobenzene	DMSO	1.8mg/mL	36284
chloroform	DMSO	0.3mg/mL	36285
cyclohexane	DMSO	19.4mg/mL	36286
1,1-dichloroethene	DMSO	40mg/mL	36287
1,2-dichloroethane	DMSO	25mg/mL	36288
cis-1,2-dichloroethylene	DMSO	4.67mg/mL	36289
trans-1,2-dichloroethylene	DMSO	4.67mg/mL	36290
1,2-dimethoxyethane	DMSO	0.5mg/mL	36291
N,N-dimethylacetamide	DMSO	5.45mg/mL	36292
N,N-dimethylformamide	DMSO	4.4mg/mL	36293
1,4-dioxane	DMSO	1.9mg/mL	36294
2-ethoxyethanol	DMSO	0.8mg/mL	36295
ethylbenzene	DMSO	1.84mg/mL	36296
ethylene glycol	DMSO	3.1mg/mL	36297
formamide	DMSO	1.1mg/mL	36298
hexane	DMSO	1.45mg/mL	36299
methanol	DMSO	15mg/mL	36401
2-methoxyethanol	DMSO	0.25mg/mL	36402
methylbutylketone	DMSO	0.25mg/mL	36400
methylcyclohexane	DMSO	5.9mg/mL	36403
methylene chloride	DMSO	3mg/mL	36404
N-methylpyrrolidone	DMSO	2.65mg/mL	36405
nitromethane	DMSO	0.25mg/mL	36406
pyridine	DMSO	1mg/mL	36407
sulfolane	DMSO	0.8mg/mL	36413
tetrahydrofuran	DMSO	3.6mg/mL	36408
tetralin	DMSO	0.5mg/mL	36409
toluene	DMSO	4.45mg/mL	36410
1,1,1-trichloroethane	DMSO	50mg/mL	36411
trichloroethene	DMSO	0.4mg/mL	36412
m-xylene	DMSO	6.51mg/mL	36414
o-xylene	DMSO	0.97mg/mL	36415
p-xylene	DMSO	1.52mg/mL	36416

DMSO = dimethyl sulfoxide

These mixtures represent the changes made in USP30/NF25 effective July 1, 2008.

**Residual Solvents - Class 1**

new!

benzene	10mg/mL	1,1-dichloroethene	40
carbon tetrachloride	20	1,1,1-trichloroethene	50
1,2-dichloroethane	25		

In dimethyl sulfoxide, 1mL/ampul  
cat. # 36279 (ea.)

These mixtures represent the changes made in USP30/NF25 effective July 1, 2008. *cont'd*

**Residual Solvents Class 2 - Mix B**

new!

(8 components)

chloroform	60µg/mL	nitromethane	50
1,2-dimethoxyethane	100	pyridine	200
n-hexane (C6)	290	tetralin	100
2-hexanone	50	trichloroethene	80

In dimethyl sulfoxide, 1mL/ampul  
cat. # 36280 (ea.)

also available

For other reference mixes for USP <467> and European Pharmacopoeia, see page 510.

These mixtures represent the changes made in USP28/NF23 effective January 1, 2005.

**Residual Solvents Class 2 - Mix A**

(15 components)

acetonitrile	2.05mg/mL	methylcyclohexane	5.90
chlorobenzene	1.80	methylene chloride	3.00
cyclohexane	19.40	tetrahydrofuran	3.45
cis-1,2-dichloroethene	4.70	toluene	4.45
trans-1,2-dichloroethene	4.70	m-xylene	6.51
1,4-dioxane	1.90	o-xylene	0.98
ethylbenzene	1.84	p-xylene	1.52
methanol	15.00		

In dimethyl sulfoxide, 1mL/ampul  
cat. # 36271 (ea.)

Class III solvents are available as custom mixes. See page 427 for our custom reference material request form.

**Residual Solvents Class 2 - Mix B**

(8 components)

chloroform	300µg/mL	nitromethane	250
1,2-dimethoxyethane	500	pyridine	1,000
n-hexane (C6)	1,450	tetralin	500
2-hexanone	250	trichloroethene	400

In dimethyl sulfoxide, 1mL/ampul  
cat. # 36272 (ea.)

free literature

USP <467> Residual Solvents Method

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Flyer  
lit. cat. # 580166

**Residual Solvents Class 2 - Mix C**

(8 components)

2-ethoxyethanol	800µg/mL	2-methoxyethanol (methyl Cellosolve®)	250
ethylene glycol	3,100	N-methylpyrrolidone	2,650
formamide	1,100	sulfolane	800
N,N-dimethylacetamide	5,450		
N,N-dimethylformamide	4,400		

In dimethyl sulfoxide, 1mL/ampul  
cat. # 36273 (ea.)

## did you know?

We prepare Rtx®-1301 (cat.# 16085) and Stabilwax® (cat.# 10640) capillary columns and the analytical reference materials to meet the requirements for European Pharmacopoeia. Download lit. cat.# 59107, *European Pharmacopoeia Analysis of Residual Solvents* from our website for more information.

## free literature

GC Analysis of Organic Volatile Impurities According to USP <467> Supplement Two of USP 25-NF 20, effective January, 2002

Download your free copy from our website!

Applications Note  
lit. cat.# 59577C

## USP &lt;467&gt; cont'd

These Class 1 mixtures represent the changes made in USP24/NF19 effective January 1, 2000, and USP23/NF18 effective January 1, 1995 to December 31, 1999. While these mixtures do not meet the current USP guidelines, many still use these mixtures to obtain a detectable benzene peak for the direct injection methods, Method I and Method V.

## USP &lt;467&gt; Calibration Mix #7

chloroform	60µg/mL	methylene chloride	600
1,4-dioxane	380	trichloroethene	80
In dimethylsulfoxide, 1mL/ampul			
cat. # 36009 (ea.)			

## USP &lt;467&gt; Calibration Mix #6

chloroform	60µg/mL	methylene chloride	600
1,4-dioxane	380	trichloroethene	80
In methanol, 1mL/ampul			
cat. # 36008 (ea.)			

## USP &lt;467&gt; Calibration Mixture #5

benzene	2µg/mL	methylene chloride	600
chloroform	60	trichloroethene	80
1,4-dioxane	380		
In dimethylsulfoxide, 1mL/ampul			
cat. # 36007 (ea.)			

## USP &lt;467&gt; Calibration Mixture #4

benzene	2µg/mL	methylene chloride	600
chloroform	60	trichloroethene	80
1,4-dioxane	380		
In methanol, 1mL/ampul			
cat. # 36006 (ea.)			

## USP &lt;467&gt; Calibration Mixture #2

benzene	100µg/mL	methylene chloride	500
chloroform	50	trichloroethene	100
1,4-dioxane	100		
In methanol, 1mL/ampul			
cat. # 36002 (ea.)			

## USP &lt;467&gt; Calibration Mixture #3

benzene	100µg/mL	methylene chloride	500
chloroform	50	trichloroethene	100
1,4-dioxane	100		
In dimethylsulfoxide, 1mL/ampul			
cat. # 36004 (ea.)			

## Ethylene Oxide

500µg/mL in dimethylsulfoxide, 1mL/ampul  
cat. # 36005 (ea.)

Ethylene oxide is available in other solvents and concentrations. Request your custom formulation at standards@restek.com.

## European Pharmacopoeia Method

The analysis of residual solvents in pharmaceutical products has changed, particularly for products being sold into Europe. The International Conference on Harmonization (ICH) Guidelines for Residual Solvents is becoming the international standard and is being adopted by more pharmacopoeias, including the United States Pharmacopoeia, every year. The ICH method and compound list is more extensive than any method previously used and poses new challenges. Compounds in Class 1 are solvents considered to be of highest risk and to be avoided in pharmaceutical manufacturing. Use of Class 2 compounds is to be limited, as they pose a lower, but present, threat to health. Compounds in Class 3 pose the lowest toxic potential and may be used routinely in manufacturing.

## European Pharmacopoeia/ICH Class 1 Mix

benzene	2µg/mL	1,1-dichloroethene	8
carbon tetrachloride	4	1,1,1-trichloroethane	1500
1,2-dichloroethane	5		
Prepared in water:dimethylsulfoxide (90:10), 1mL/ampul			
cat. # 36228 (ea.)			

## European Pharmacopoeia/ICH Class 1 Mix (revised)

benzene	2µg/mL	1,1-dichloroethene	8
carbon tetrachloride	4	1,1,1-trichloroethane	10
1,2-dichloroethane	5		
In water:dimethylsulfoxide (90:10), 1mL/ampul			
cat. # 36261 (ea.)			

## European Pharmacopoeia/ICH Q3C(M) Class 2 Mix A

2-ethoxyethanol	160µg/mL	N-methylpyrrolidone	530
ethylene glycol	620	sulfolane	160
formamide	220		
2-methoxyethanol (methyl Cellosolve®)	50		
In dimethyl sulfoxide, 1mL/ampul			
cat. # 36275 (ea.)			

## European Pharmacopoeia/ICH Class 2

<b>Mix B (10 components)</b>			
acetonitrile	410µg/mL	methanol	3,000
chloroform	60	nitromethane	50
1,2-dimethoxyethane	100	pyridine	200
N,N-dimethylacetamide	1,090	1,2,3,4-tetrahydronaphthalene (tetraline)	100
1,4-dioxane	380		
2-hexanone	50		
Prepared in water:dimethylsulfoxide (90:10), 1mL/ampul			
cat. # 36230 (ea.)			

## European Pharmacopoeia/ICH Q3C(M)

<b>Class 2 Mix C (14 components)</b>			
chlorobenzene	360µg/mL	methylene chloride	600
cyclohexane	3,880	tetrahydrofuran	720
cis-1,2-dichloroethene	1,870	toluene	890
N,N-dimethylformamide	880	trichloroethene	80
ethylbenzene	369	m-xylene	1,302
n-hexane (C6)	290	o-xylene	195
methylcyclohexane	1,180	p-xylene	304
In dimethyl sulfoxide, 1mL/ampul			
cat. # 36274 (ea.)			