

# Revised USP 467 Residual Solvent Method

## Satisfy New Method Requirements with Restek Columns and Standards

By Rick Lake, Pharmaceutical Innovations Chemist

- Overview of the new USP 30/NF 25 procedure.
- New reference standards - stock mixes, custom preparations.
- Optimize your testing within the constraints of the method.

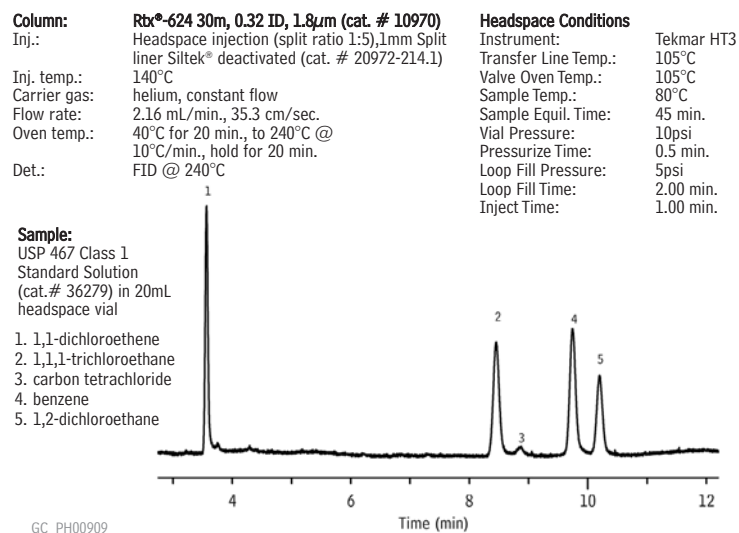
Organic volatile impurities (OVIs), commonly referred to as residual solvents, are trace level chemical residues in drug substances and drug products that are byproducts of manufacturing, or that form during packaging and storage. The United States Pharmacopeia recently revised the general chapter on residual solvent analysis, USP 467, to mirror the International Conference on Harmonization (ICH) guidelines. This revision, effective July 1, 2007, replaces previous methods that were not consistent with the ICH guidelines.

The revised procedure consists of a static headspace extraction coupled with a gas chromatographic separation and flame ionization detection (GC/FID), and is divided into two sections based on sample solubility – water soluble and water insoluble articles. Altogether, the test method consists of three separate procedures – A, B and C – that are designed to identify, confirm and quantify residual solvents in pharmaceuticals.

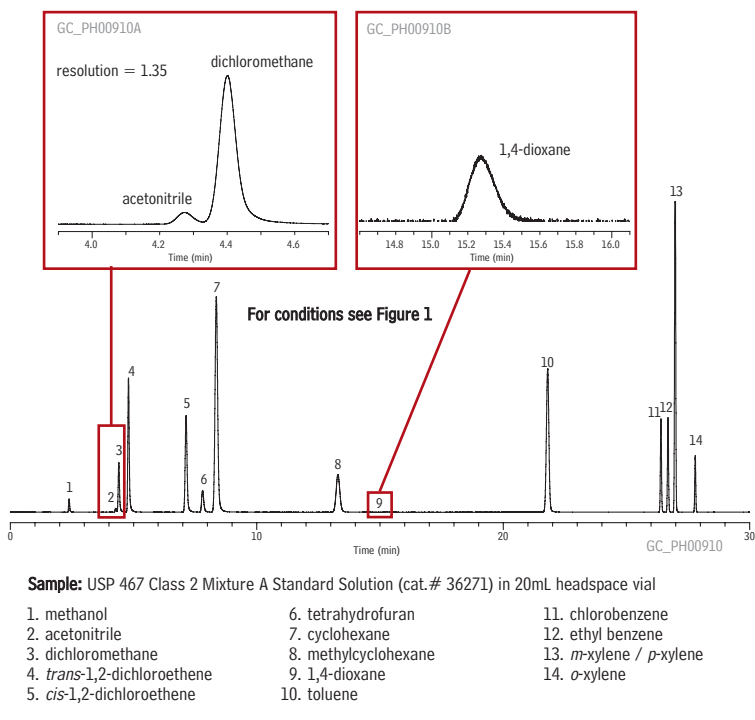
Procedure A is the first step in the identification process and is performed to screen samples for residual solvents. A series of residual solvent mixes, consisting of Class 1 and Class 2 mixes A and B, are analyzed along with the system suitability and test solutions on an Rtx®-624 column – equivalent to an Rtx®-1301 (G43) column (Figures 1-3). If a peak in the sample matches a retention time, and exceeds the response of the corresponding standard, the analyst proceeds to Procedure B for verification of the analyte.

Once a residual solvent is identified, Procedure B is performed to confirm analyte identity. We recommend a Stabilwax® (G16) capillary column as a confirmation column because it yields an alternate selectivity compared to an Rtx®-624 column or an Rtx®-1301 (G43) column. (See our OVI retention time index at [www.restek.com/ovi](http://www.restek.com/ovi)). The same reference mixes are analyzed with an acetonitrile/trichloroethylene system suitability solution. If a residual solvent is verified, Procedure C is used to quantify the analyte by comparison to a specific, individual standard for the analyte identified. For water-insoluble articles, the procedure is the same, except dimethylformamide and 1,3-dimethyl-2-imidazolidinone are used as the diluent and Class 2 Mix C (higher boiling point solvents mix) is analyzed as a reference solution.

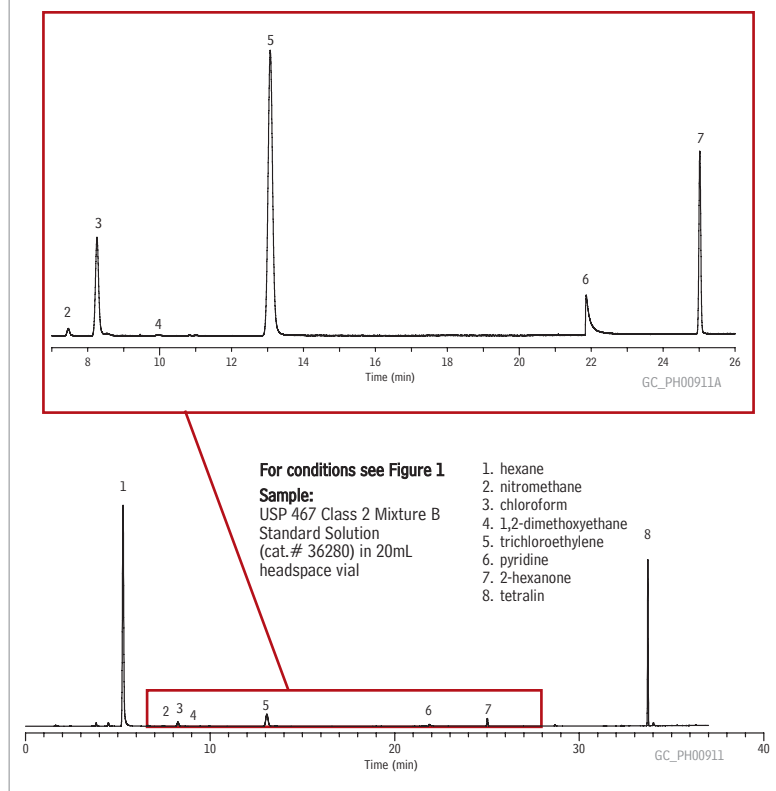
**Figure 1** USP Residual Solvent Class 1 standard solution on an Rtx®-624 (G43) column.



**Figure 2** USP Residual Solvent Class 2 Mixture A standard solution on an Rtx®-624 (G43) column.



**Figure 3** USP Residual Solvent Class 2 Mixture B standard solution on an Rtx®-624 (G43) column.



## did you know?

Restek offers a full day seminar on headspace analysis. Join us September 26, in Edison, NJ for a day of learning focused exclusively on headspace principles, techniques, and applications (cat.# 65563). To register, visit us online at [www.restek.com/seminar](http://www.restek.com/seminar)

## for more info

- Technical poster:  
*Comprehensive Dual-Column Analysis of Residual Solvents in Water-soluble Articles Using Dynamic Headspace and Modular Accelerated Column Heating.*  
[www.restek.com/usp467](http://www.restek.com/usp467)
- A Technical Guide for Static Headspace Analysis Using GC, cat.# 59895A.
- OVI retention time index  
[www.restek.com/ovi](http://www.restek.com/ovi)

### Rtx®-624 (G43) Columns (fused silica)

(Crossbond® 6% cyanopropylphenyl/94% dimethyl polysiloxane)

ID	df (µm)	temp. limits	length	cat. #
0.32mm	1.80	-20 to 240°C	30-Meter	10970
0.53mm	3.00	-20 to 240°C	30-Meter	10971

### Stabilwax® (G16) Columns (fused silica)

(Crossbond® Carbowax® polyethylene glycol)

ID	df (µm)	temp. limits	length	cat. #
0.32mm	0.25	40 to 250°C	30-Meter	10624
0.53mm	0.25	40 to 250°C	30-Meter	10625

### Siltek® 1mm Split Liners for Agilent GCs

Use this liner for increased sensitivity. Exclusive Siltek® deactivation makes liner inert to active sample components.

Benefits/Uses:	ID*/OD & Length (mm)	cat.# ea.	cat.# 5-pk.
for purge & trap inlet splitting or sample <1µL	1.0 ID 6.3 OD x78.5	20972-214.1	20973-214.5

\*Nominal ID at syringe needle expulsion point.

Restek can supply all your USP 467 materials and can help you optimize your testing within the constraints of the method. Visit us on the web at [www.restek.com](http://www.restek.com) or contact our Technical Support team at 800-356-1688, ext.4, for solutions to your residual solvent testing needs and tips on optimizing your analysis.

### Residual Solvents - Class 1

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

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

### 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-dichloroethylene	4.70	toluene	4.45
trans-1,2-dichloroethylene	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.)

### Residual Solvents Class 2 - Mix B (8 components)

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

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

## New singles & custom mixes for USP testing!

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