Revised USP General Chapter Monograph <467>: Residual Solvents

Sky Countryman
Phenomenex, Inc., 411 Madrid Ave., Torrance, CA 90501 USA

Satisfy new method requirements using the proper tools and products.

Background

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. It is the responsibility of the drug manufacturers to ensure that these residues are removed, or are present only in limited concentrations.

The United States Pharmacopeia (USP) recently revised the general chapter on residual solvent analysis, USP <467>, to reflect the International European Pharmacopoeia (EP) guidelines for the identification, control and quantification of residual solvents. This revision, effective July 1, 2008, replaces previous methods and significantly increases the requirements with which a pharmaceutical company must comply in order to demonstrate that *all drug products* (not just new) are compliant with Chapter <467> limits. The change increases the number of solvents requiring testing from seven to *fifty-nine*.

While most companies have extensive data on the solvents used in the manufacturing of their API, the information regarding solvents present in the excipients is usually much lower.

Testing is only required for those solvents used in the manufacturing or purification process of drug substances, excipients or products. This allows each company to determine which solvents it uses in production and develop testing procedures that address their specific needs.

Solvents have been classified based on their potential health risks into three main categories:

- Class 1: Solvents should not be used because of the unacceptable toxicities or deleterious environmental effects
- Class 2: Solvents should be limited because of inherent toxicities
- Class 3: Solvents may be0 regarded as less toxic and of lower risk to human health

Overview of Method

The USP has provided a method for the identification, control and quantification of Class 1 and 2 residual solvents. The method calls for a gas chromatograph (GC) analysis with flame ionization detection (FID) and a headspace injection from either water or organic diluent. The monograph has suggested two procedures for qualitative analysis: *Procedure A* specifies a G43 (Zebron ZB-624 or equivalent) phase and *Procedure B* specifies a G16 (Zebron ZB-WAX*plus* or equivalent) phase. *Procedure C* is for quantitative analysis.

Procedure A should be used first. If a compound is determined to be above the specified concentration limit, then Procedure B should be used to confirm its identity. Since there are known co-elutions on both phases, the orthogonal selectivity ensures that co-elutions on one phase will be resolved on the other. Neither procedure is quantitative, so to determine the concentration, the monograph specifies Procedure C, which utilizes whichever phase will give the fewest co-elutions

Procedure A:	G43 (6 %-cyanopropy - 94 % dimethylpolysiloxane
Procedure B:	G16 (Polyethylene Glycol)
Procedure C:	G43 or G16 depending on which gave fewer co-elutions

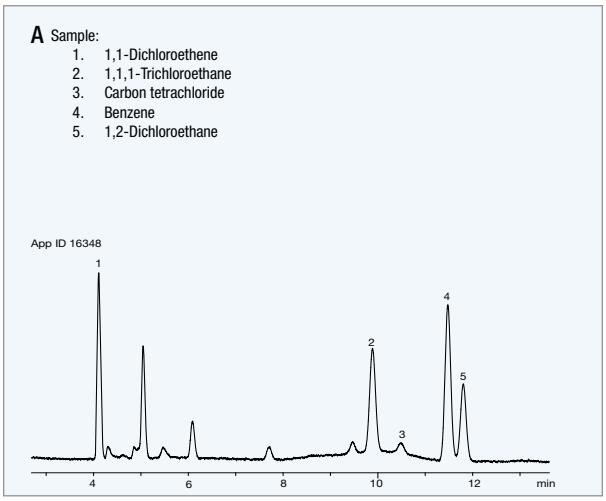
All procedures were performed using a Shimadzu 2010 GC System, an Overbrook Scientific HT200H Headspace Autosampler and Phenomenex Zebron GC Columns.

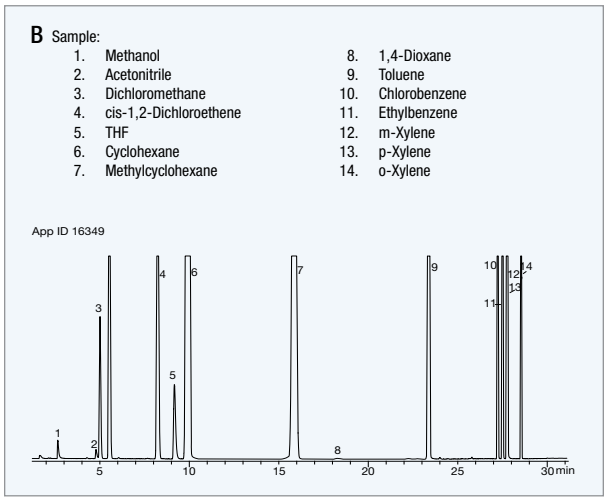
Procedure A – Identification (Class 1 & 2 Solvents)
System Suitability Requirements:

- Signal-to-noise ratio of 1, 1, 1-trichloroethane > 5
- Signal-to-noise ratio of each peak of each Class 1 solvent should be > 3
- Resolution between acetonitrile and methylene chloride > 1.0

At the concentration limits specified by the monograph, signal-to-noise ratio for 1, 1, 1-trichloroethane was 59.9; and all other compounds exceeded 3. Resolution between acetonitrile and methylene chloride was 1.71.

Conditions same for all runs
Column: Zebron ZB-624
Dimensions: 30 meter x 0.32 mm x 1.8 µm
Part No.: 7HM-G005-31
Injection: Split 5:1 @ 140 °C, 1 mL
Carrier Gas: Helium @ 35 cm/sec (constant flow)
Oven Program: 40 °C for 20 min to 240 °C @ 10 °C/min for 20 min
Detector: FID @ 250 °C





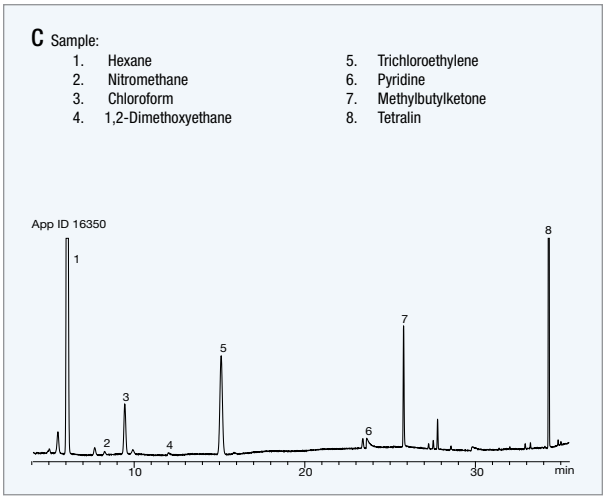


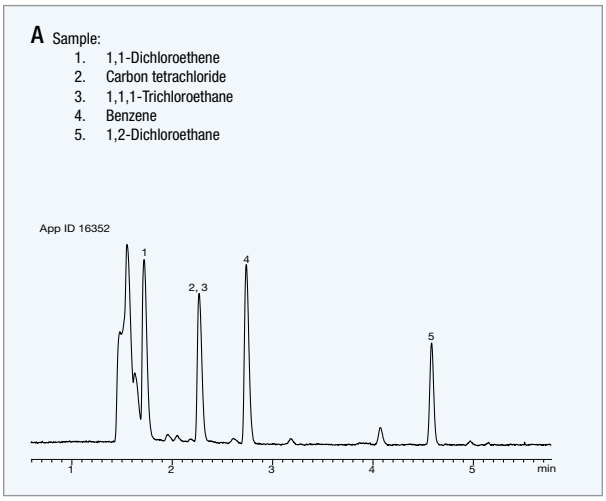
Figure 1.
USP Method <467> Procedure A.
A) Class 1 for water soluble compounds.
B) Class 2 mix A for water soluble compounds.
C) Class 2 mix B for water soluble compounds.

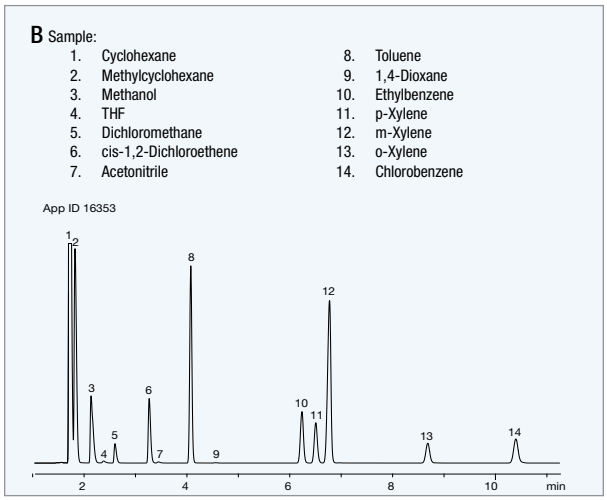
Procedure B – Confirmation (Class 2 & 3 Solvents)
System Suitability Requirements:

- Signal-to-noise ratio of benzene > 5
- Signal-to-noise ratio of each peak of each Class 1
- Solvent should be > 3
- Resolution between acetonitrile and trichloroethylene is > 1.0

At the concentration limits specified by the monograph, signal-to-noise ratio for benzene was 104.2; and all other compounds exceeded 3. Resolution between acetonitrile and trichloroethylene was 1.52.

Conditions same for all runs
Column: Zebron ZB-WAX$_{PLUS}$
Dimensions: 30 meter x 0.32 mm x 0.25 µm
Part No.: 7HM-G013-11
Injection: Split 5:1 @ 140 °C, 1 mL
Carrier Gas: Helium @ 2.1 mL/min (constant flow)
Oven Program: 50 °C hold 20 min to 165 °C @ 6 °C/min hold 20 min
Detector: FID @ 250 °C





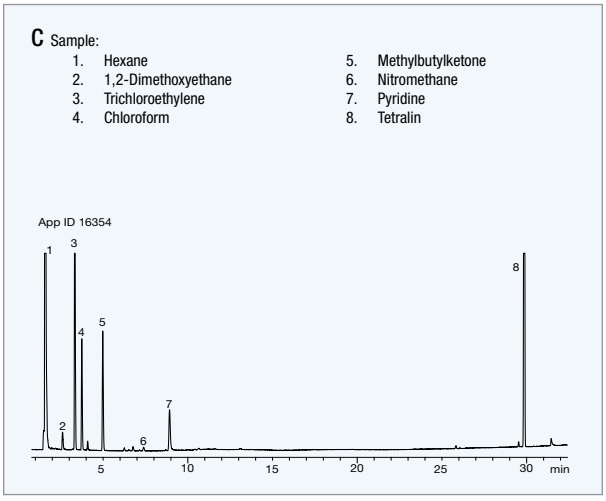


Figure 2.
USP Method <467> Procedure B.
A) Class 1 for water soluble compounds.
B) Class 2 mix A for water soluble compounds.
C) Class 2 mix B for water soluble compounds.

Australia
t: 02-9428-6444
f: 02-9428-6445
auinfo@phenomenex.com

Austria
t: 01-319-1301
f: 01-319-1300
anfrage@phenomenex.com

Belgium
t: +31 (0)30-2418700
f: +31 (0)30-2383749
beinfo@phenomenex.com

Canada
t: (800) 543-3681
f: (310) 328-7768
info@phenomenex.com

Denmark
t: 4824 8048
f: 4810 6265
dkinfo@phenomenex.com

France
t: 01 30 09 21 10
f: 01 30 09 21 11
franceinfo@phenomenex.com

Germany
t: 06021-58830-0
f: 06021-58830-11
anfrage@phenomenex.com

Ireland
t: 01 247 5405
f: +44 1625-501796
eireinfo@phenomenex.com

Italy
t: 051 6327511
f: 051 6327555
italiainfo@phenomenex.com

Luxembourg
t: +31 (0)30-2418700
f: +31 (0)30-2383749
nlinfo@phenomenex.com

Netherlands
t: 030-2418700
f: 030-2383749
nlinfo@phenomenex.com

New Zealand
t: 09-4780951
f: 09-4780952
nzinfo@phenomenex.com

Puerto Rico
t: (800) 541-HPLC
f: (310) 328-7768
info@phenomenex.com

United Kingdom
t: 01625-501367
f: 01625-501796
ukinfo@phenomenex.com

All other countries:
Corporate Office USA
t: (310) 212-0555
f: (310) 328-7768
info@phenomenex.com

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Conclusion

Since the deadline for the USP <467> revision has passed, all pharmaceutical companies need to determine as soon as possible how the changes to General Chapter <467> will impact their testing procedures. The more excipients and excipient vendors a company uses, the more it will be to demonstrate compliance with the new methodology.

The new USP regulations are aimed at improving patient safety and will need to be implemented for all products, existing or new. Although the USP has provided a testing method that can be used to identify and quantitate Class 1 and 2 solvents, the method can be improved based on each companies' needs. Only those solvents used in the manufacturing process must be tested in the final dosage form.

For the best solution, each company must consider the number of samples, analysis time, method validation, accuracy, precision and cost of equipment. Once method performance has been achieved, it is also important to consider if that method can be transferred to other manufacturing facilities. Do they have the knowledge and instrumentation to implement the method?

The changes to the <467> monograph came into effect on July 1, 2008 so it is critical to start formulating a strategy now to become compliant. During the process, there is no doubt that other questions and concerns will arise. To ensure the USP addresses as many of these concerns as possible in the new method, an open dialog between industry and the USP is critical.

All products and instruments used in this technical note have been shown to reliably provide resolution and signal-to-noise ratio, as specified revised monograph. The Phenomenex Zebron GC columns provided the low bleed level needed to meet system suitability. The HT200H Headspace Autosampler was made to meet the needs of static headspace injection for GC analysis. This economical autosampler operates with all major GC systems, including Agilent, Shimadzu and Varian.

For more information about Phenomenex's Zebron GC columns, email info@Phenomenex.com. For more information or to obtain literature and specifications on the HT200H Headspace Autosampler, please contact Overbrook Scientific at 617.364.7683 or visit our website at www.overbrookscientific.com

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