Understanding the Revisions to USP Monograph <467>: Residual Solvents

Sky Countryman
Product Manager, Gas Chromatography Products
Phenomenex Inc., Torrance, CA, USA

Introduction

In 1988, the United States Pharmacopoeia (USP) provided control limits and testing criteria for seven organic volatile impurities (OVIs) under official monograph <467>. The compounds were chosen based on relative toxicity and only applied to drug substances and some excipients. In an effort to harmonize with the International Conference for Harmonization (ICH), the USP has proposed the adoption of a slightly modified version of Quality-3C (Q3C) methodology, which has been scheduled for implementation on July 1, 2007.

The ICH Q3C methodology provides a risk-based approach to residual solvent analysis that considers a patient's exposure to a solvent residue in the drug product. Solvents have been classified based on their potential health risks into three main classes:

- 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 be regarded as less toxic and of lower risk to human health

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.

It is the responsibility of the drug manufacturer to qualify the purity of all the components used in the manufacturing of the drug product. This would pertain to items such as excipients, of which some contain residual levels of Class 1 solvents by nature of the manufacturing process and/or nature of the starting materials (e.g. ethyl cellulose).

The new <467> monograph provides an optional method to determine when residual solvent testing is required for Class 2 solvents. Each Class 2 solvent is assigned a permitted daily exposure (PDE) limit, which is the pharmaceutically acceptable intake level of a residual solvent. When the solvent level in drug substances, excipients, and drug product are below the PDE limit for a given solvent, testing is not required when the daily dose is <10 grams. When the level of solvent is expected to be above the PDE limit, testing would be required to determine if the solvent was removed during the formulation process.

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 chromatographic (GC) analysis with flame ionization detection (FID) and a headspace injection from either water or organic diluent. The monograph has suggested two procedures: Procedure A G43 (Zebron ZB-624) phase and Procedure B G16 (Zebron ZB-WAXplus) phase. 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.

Class 3 solvents may be determined by <731> Loss on Drying unless the level is expected to be >5000 ppm or 50 mg. If the loss on drying is >0.5 %, then a water determination should be performed using <921> Water Determination.

The monograph allows the use of alternative methodologies as long as they have been appropriately validated. However, only the results obtained by the procedures given in the general chapter are conclusive. So, the results from the alternate method will have to be compared to the monograph before they will be acceptable to the Food and Drug Administration (FDA). Some concern was raised by industry at the USP/PDA Joint Conference on residual solvents in January 2007 about the monograph's performance for certain compounds. If the monograph were not suitable, comparison of the alternative method to the monograph would be impossible.

Implementation

The USP has written the new <467> monograph to include most of the concepts and acceptance criteria of the ICH Q3C guidelines, however there are changes. It is these subtle changes in text that have created some confusion about what companies must do to meet the new guidelines. One of the most important considerations is that once implemented, the new method will pertain to all currently marketed drug products as well as those in development and clinical trials. In many cases, this will require re-submission for existing validations.

In 1997, the European Union (EU) adopted ICH guidelines. In 2000, they started requiring that all currently marketed drug products, as well as those in development or clinical trial, meet the ICH guidelines. Although there was some initial uncertainty, most companies found that their products met Q3C guidelines without manufacturing changes.

The biggest question to be answered is whether the changes the USP has made will be significant enough to require companies to revisit validations which currently meet ICH Q3C guidelines. The USP is currently discussing and deciding if last minute changes to the monograph will be necessary.

USP Method <467> Performance

GC Analysis

The USP <467> monograph references Procedures A and B for qualitative analysis and Procedure C for quantitative analysis. The two column approach is designed to reduce misidentifications since there are known co-elutions on both phases. Figures 1 & 2 show the performance of each solvent class using both Procedures A and B using the water-soluble option. Performance criteria for each method and the results obtained are discussed below.

Class 1 & 2 Solvents: Procedure A

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 545, and all other compounds exceeded 3. Resolution between acetonitrile and methylene chloride was 1.98.

Class 2 & 3 Solvents: Procedure B

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 6341, and all other compounds exceeded 3. Resolution between acetonitrile and trichloroethylene was 2.78.

Optimizing the GC Method

Following the conditions specified by the monograph, the total analysis time for all three samples would be >3 hours. It isn't feasible for most companies to spend 3 hours per sample to get identification and quantitation of all target analytes. In a QC department, sample throughput and instrument stability are the primary concerns, therefore most labs have validated their own testing methodologies based on <467> requirements.

When choosing the appropriate column dimensions for a specific set of target analytes, there are four main variables that need to be considered:

1. Length (L)
2. Internal Diameter (ID)
3. Film Thickness (df)
4. Stationary Phase Composition

Of the four variables, stationary phase will have the biggest impact on column selectivity. In order to remain consistent with the <467> monograph, a lab should try to work with those phases listed in section <621> of the USP guidelines. The G43 and G16 phases are well suited for solvent analysis and by choosing more efficient column dimensions a lab should be able to resolve all target analytes in less than 20 minutes.

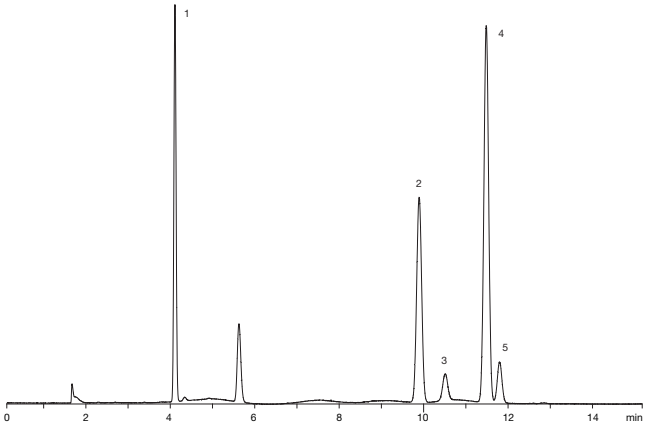
Figure 1. USP Method <467> Procedure A for water-soluble compounds.

App ID 16004

Residual Solvents:
USP Method 467-Class 1

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
Sample:	All analytes 2 ppm in DMSO

1. 1,1-Dichloroethene
2. 1,1,1-Trichloroethane
3. Carbon tetrachloride
4. Benzene
5. 1,2-Dichloroethane



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Residual Solvents:
USP Method 467-Class 2

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 @ 3.5 cm/sec (constant flow)
Oven Program:	40 °C for 20 min to 240 °C @ 10 °C/min for 20 min
Detector:	FID @ 250 °C
Sample:	All analytes are at 50 ppm in DMSO

1. Methanol
2. Acetonitrile
3. Dichloromethane
4. Hexane
5. cis-1,2-Dichloroethene
6. Nitromethane
7. Chloroform
8. Cyclohexane
9. 1,2-Dimethoxyethane
10. 1,1,2-Trichloroethene
11. Methylcyclohexane
12. 1,4-Dioxane
13. Toluene
14. Pyridine
15. Methylethyl ketone
16. Chlorobenzene
17. N,N-Dimethylformamide
18. Ethylbenzene
19. m-Xylene
20. p-Xylene
21. o-Xylene
22. Tetralin®

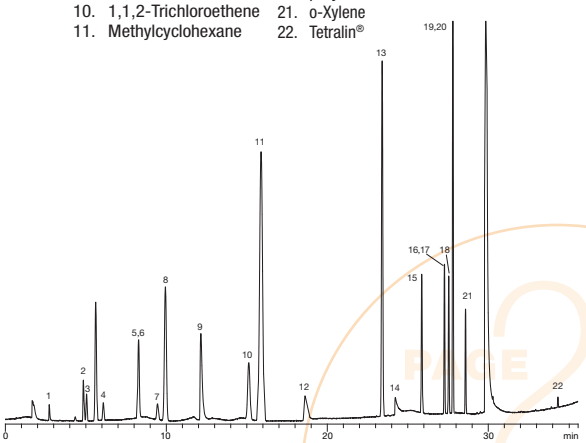
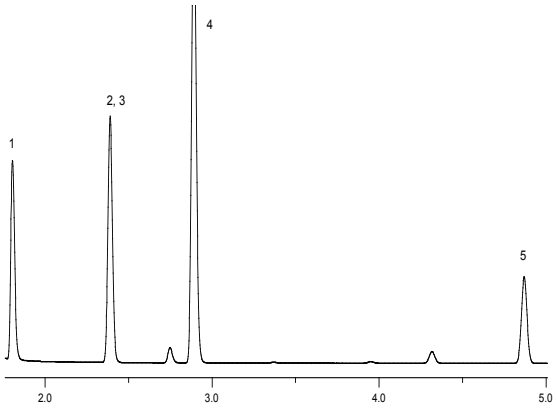


Figure 2. USP Method <467> Procedure B for water-soluble compounds.

App ID 16243

Residual Solvents:
USP Method 467-Class 1

Column:	Zebron ZB-WAXplus
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 @ 35 cm/sec (constant flow)
Oven Program:	50 °C hold 20 min to 165 °C @ 6 °C/min hold 20 min
Detector:	FID @ 250 °C
Sample:	1. 1,1-Dichloroethene 2. Carbon tetrachloride 3. 1,1,1-Trichloroethane 4. Benzene 5. 1,2-Dichloroethane



App ID 16244

Residual Solvents:
USP Method 467-Class 2

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 @ 35 cm/sec (constant flow)
Oven Program:	50 °C for 20 min to 165 @ 6 °C/min hold 20 min
Detector:	FID @ 250 °C
Sample:	1. Cyclohexane 2. Methylcyclohexane 3. Methylene chloride 4. 1,2-Dimethoxyethane 5. cis-1,2-Dichloroethene 6. Trichloroethylene 7. Acetonitrile 8. Chloroform 9. Toluene 10. 1,4-Dioxane 11. Methylbutylketone 12. Ethylbenzene 13. p-Xylene 14. m-Xylene 15. Nitromethane 16. o-Xylene 17. Pyridine 18. Chlorobenzene 19. Tetralin

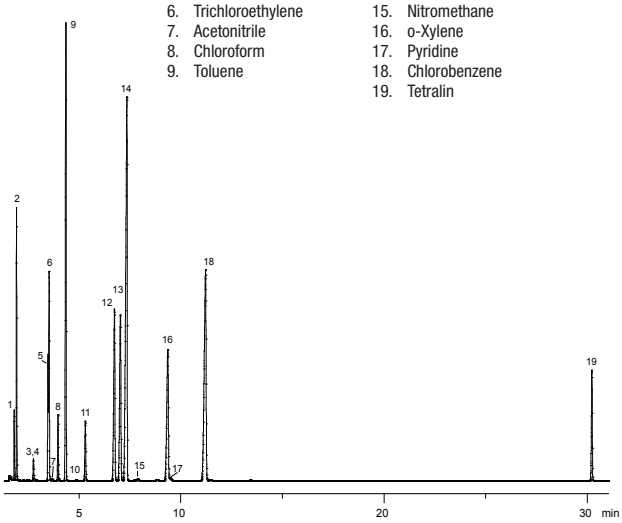


Figure 3. Separation of 18 solvents from Class 1, 2, and 3 using a G16 equivalent phase.

App ID 16140

Solvent Analysis:
ASTM Method D 5135-95

Column:	Zebron ZB-WAXplus
Dimensions:	30 meter x 0.25 mm x 0.25 µm
Part No.:	7HG-G013-11
Injection:	Split 100:1 @ 250 °C, 0.5 µL
Carrier Gas:	Helium @ 1.6 mL/min (constant flow)
Oven Program:	35 °C (hold 3 min) to 95 °C @ 20 °C/min (hold 8 min)
Detector:	FID @ 260 °C
Sample:	1. Pentane 2. Methyl formate 3. Acetone 4. Ethyl acetate 5. Methyl ethyl ketone 6. Methanol 7. 2-Methyl-2-propanol 8. Methylene chloride 9. Benzene 10. Ethanol 11. 2-Butanol 12. Toluene 13. Propanol 14. Ethylbenzene 15. p-Xylene 16. m-Xylene 17. 1-Butanol 18. o-Xylene

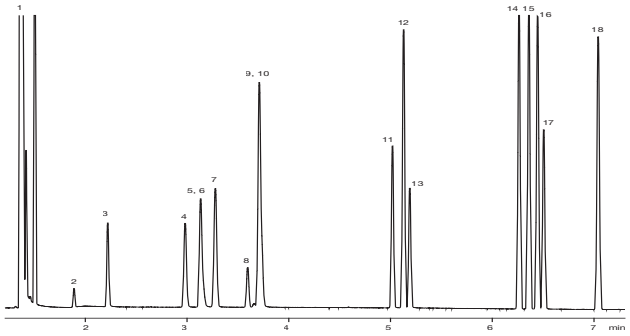
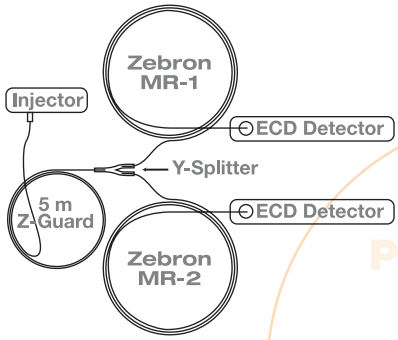


Figure 3 shows the separation of 18 solvents from Class 1, 2, and 3 using a G16 equivalent phase. Column length and internal diameter were chosen to achieve maximum resolving power with minimal analysis time. Choosing these conditions allowed the method to be completed in less than 8 minutes with a total cycle time of less than 10 minutes.

Using this method, the results would still need to be confirmed using a G43 phase and then quantitated. The total analysis time is much less using this method, but it still requires three separate tests to confirm and quantitate all compounds. This three-test approach will always be required when using the method specified FID because it does not give any information about the peaks identity. To eliminate the three-test approach would require using both G43 and G16 phases in parallel or simply using a mass spectrometer (MS) detector.

Dual column analysis where two phases are connected in parallel using a 5-10 meter guard column and a "Y" – union are commonplace in environmental testing.



By making one injection and splitting the sample into two columns, both Procedure A and Procedure B can be accomplished at the same time. If a calibration curve is run before each batch of samples and a suitable calibration check is run after each batch of samples to verify the stability of the calibration, then Procedure C could also be run at the same time. The main obstacle of using this type of system is to use one oven program to separate the target analytes on two column phases.

While dual column approaches are widely used and accepted, the decreasing cost of bench top GC/MS systems make this a much more viable long-term solution. The main advantage of GC/MS is the spectral confirmation it provides of each peak. MS data is widely used and accepted throughout the world and eliminates any possible misidentifications.

The chromatographic advantage of GC/MS is that it is able to distinguish co-eluting peaks based on the mass fragmentation pattern. This allows many more compounds to be separated in a shorter time. By choosing the appropriate column phase and dimension, it is possible to develop a fast, sensitive, accurate and definitive testing method for all Class 1, 2, and 3 solvents simultaneously (Figure 4). Table 1 shows the co-eluting compounds and their mass ions. Only peaks 17 & 18 have the same mass, however both are Class 3 solvents and would only need to be confirmed if the level was about 5,000 ppm.

Figure 4. Screening of Class 1, 2, and 3 solvents using GC/MS.

App ID 15926

Solvent Analysis: ZB-WAXplus

Column:	Zebron ZB-WAXplus
Dimensions:	30 meter x 0.25 mm x 0.25 µm
Part No.:	7HG-G013-11
Injection:	Split 50:1 @ 220 °C, 0.2 µL
Carrier Gas:	Helium @ 1.2 mL/min (constant flow)
Oven Program:	30 °C for 1 min to 70 °C @ 14 °C/min to 220 °C @ 25 °C for 3 min
Detector:	MSD @ 250 °C

Sample:

1. Air
2. Pentane
3. Hexane
4. Ethyl ether
5. 2-Methoxy-2-methyl-2-propane (MTBE)
6. Heptane
7. Cyclohexane
8. 1,1-Dichloroethene
9. Methylcyclohexane
10. Acetone
11. Formic acid ethyl ester (Ethyl formate)
12. Acetic acid methyl ester (Methyl acetate)
13. Tetrahydrofuran (THF)
14. Carbon tetrachloride
15. 1,1,1-Trichloroethane
16. Ethyl acetate
17. Acetic acid-1-methyl ethyl ester
18. 2-Butanone (MEK)
19. 1,2-Dimethoxyethane
20. Dichloromethane
21. Isopropanol
22. Benzene
23. Propyl acetate
24. 1,2-Dichloroethene
25. Trichloroethylene
26. Acetonitrile
27. Methylisobutylketone (MIBK)
28. Isobutyl acetate
29. Chloroform
30. Toluene
31. n-Propanol
32. Water
33. 1,4-Dioxane
34. 1,2-Dichloroethane
35. Butyl acetate
36. 2-Hexanone (MBK)
37. 2-Methylpropanol
38. Ethylbenzene
39. p-Xylene
40. m-Xylene
41. Butanol
42. Nitromethane

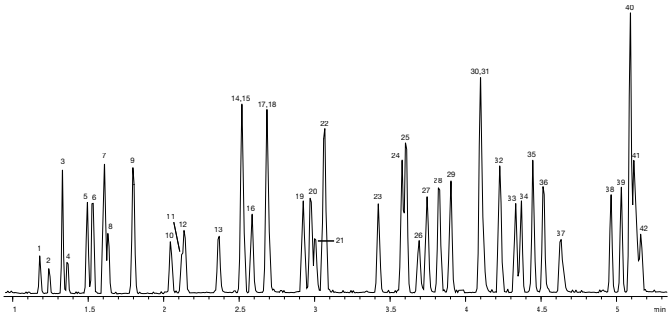


Table 1. Mass ions for co-eluting peaks.

Peak	Compound	Mass Ion
11	Ethyl Formate	31
12	Methyl Acetate	43
14	Carbon Tetrachloride	117
15	1,1,1-Trichloroethane	97
17	Isopropyl Acetate	43
18	MEK	43
30	Toluene	91
31	N-Propanol	31
40	m-Xylene	91/106
41	Butanol	56
42	Nitromethane	30

Conclusion

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 & 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 will not be official until July, but it is important 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.

For more information about this subject or to learn about additional ways to become compliant, contact your local Phenomenex representative or visit www.phenomenex.com.

ORDERING INFORMATION

Part No.	Description
7HM-G005-31-TN	ZB-624, 30 m x 0.32 mm, 1.80 µm
7HK-G005-36-TN	ZB-624, 30 m x 0.53 mm, 3.00 µm
7HG-G013-11-TN	ZB-WAX*plus*, 30 m x 0.25 mm x 0.25 µm
7HM-G013-11-TN	ZB-WAX*plus*, 30 m x 0.32 mm x 0.25 µm
7HK-G013-11-TN	ZB-WAX*plus*, 30 m x 0.53 mm x 0.25 µm

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