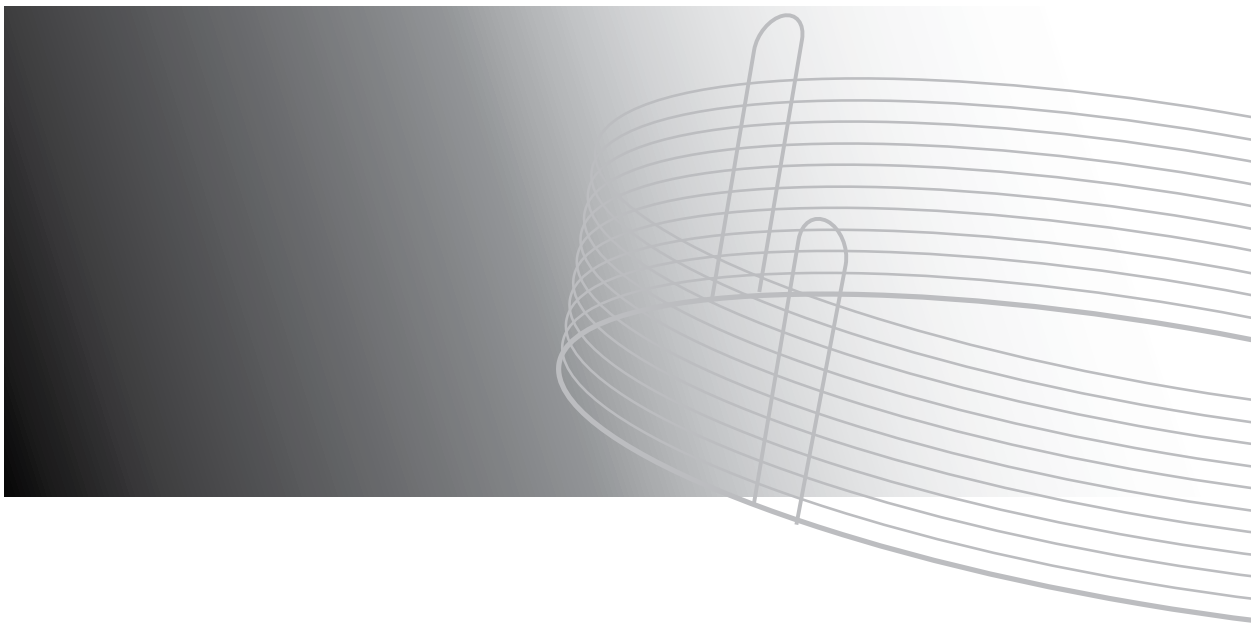

Understanding the Revisions to USP Monograph <467>: Residual Solvents

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Abstract

The United States Pharmacopoeia (USP) has published in USP Volume 30 that there will be a major revision to Monograph <467> effective July 1, 2008. The change increases the number of solvents requiring testing from seven to fifty-nine. Each solvent has been assigned a concentration limit in the final drug product based on its potential health risk. The USP has proposed three testing procedures to identify and quantitate the amount of drug in the final product. This paper will discuss the impact these new revisions will have on existing and new validated testing procedures. The performance of the USP methods is evaluated and the use of other properly validated methodologies is discussed.

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.[1] 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, 2008.

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.[2] 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 toxicity or deleterious environmental effects
- Class 2: Solvents should be limited because of inherent toxicity
- 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).[3]

1. Identification, Control, and Quantification of Residual Solvents

The USP has provided a method for the identification, control, and quantification of Class 1 and 2 residual solvents.[4] 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 specifies a G43 (Zebron ZB-624, or equivalent) phase and Procedure B specifies a G16 (Zebron ZB-WAX$_{PLUS}$, or equivalent) 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.

- Procedure A: G43 (6 %-cyanopropyl – 94 % dimethylpolysiloxane)
- Procedure B: G16 (Polyethylene Glycol)
- Procedure C: G43 or G16 depending on which gave fewer 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.

USP monograph <467> 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.

Optional Methods for Determining Levels of Class 2 Residual Solvents

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.

Impact of the New <467> Monograph

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 differences between the two methodologies. 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.

The European Union (EU) adopted ICH guidelines in 1997 and has required all currently marketed drug products, as well as those in development or clinical trial to meet the ICH guidelines since 2000. Although there was some initial uncertainty, most companies found that their products met Q3C guidelines without manufacturing changes.[5]

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.

There are currently marketed drug products that are known to contain solvent levels above the required limits. In cases where it is impossible or not feasible to remove the solvent, a company should work with the FDA to determine a course of action. This may involve granting an exception for a specific formulation. However, decisions will be made on a case-by-case basis depending on various criteria.

The control limits for solvent testing were formulated based on the potential risks when the drug is administered orally. The exposure limit might not be appropriate for topical applications and/or consumer products. As of now, the USP has made no distinction between the products, but has said it is reviewing the matter based on industry feedback.

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 Procedure A and Procedure B using the water-soluble and non water-soluble options. Performance criteria for each method and the results obtained are discussed on pages 4 and 5.

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 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

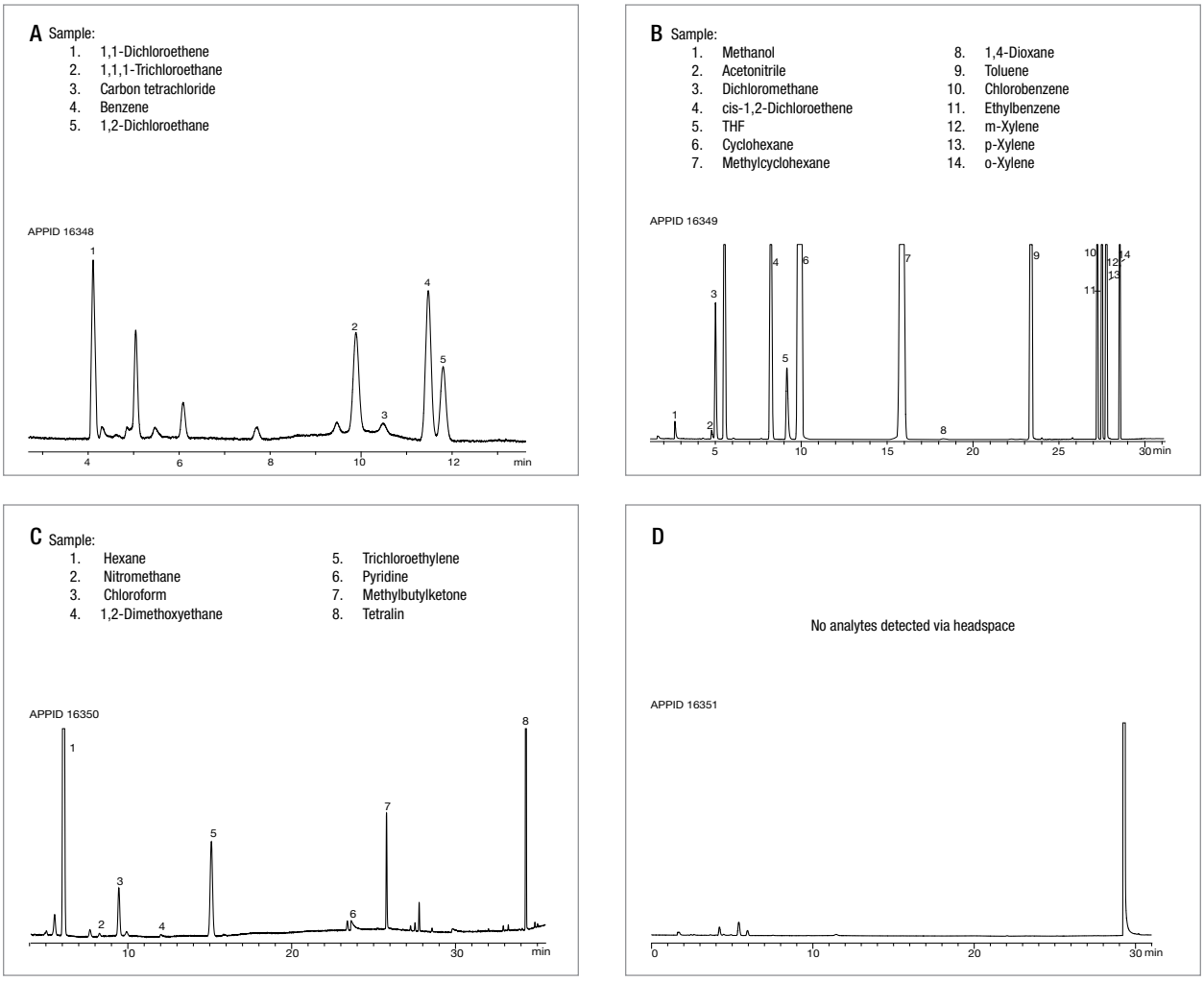

Figure 1. USP Method <467> Procedure A. A) Class 1 for water soluble compounds. B) Class 2 mix A for water soluble compounds. C) Class 2 mix B for water soluble compounds. D) Class 3 mix C for water non-soluble compounds.

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 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 ºC, 1 mL
Carrier Gas:	Helium @ 2.1 mL/min (constant flow)
Oven Program:	50 ºC hold 20 min to 165 ºC @ 6 ºC/min hold 20 min
Detector:	FID @ 250 °C

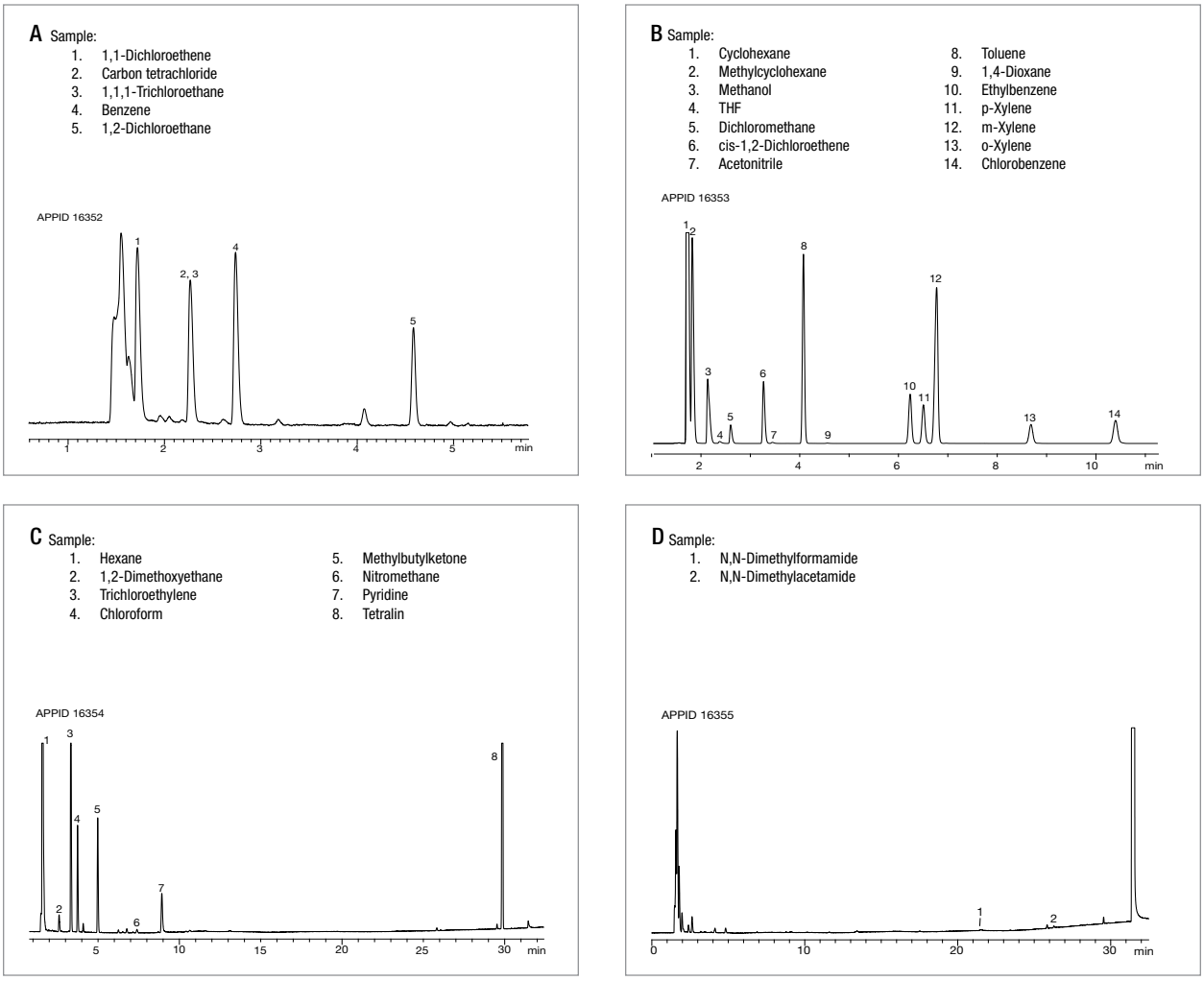

Figure 2. USP Method <467> Procedure B. A) Class 1 for water soluble compounds. B) Class 2 mix A for water soluble compounds. C) Class 2 mix B for water soluble compounds. D) Class 3 mix C for water non-soluble compounds.

2. A Strategic Approach to the Testing of Residual Solvents That Meets <467> Guidelines

Although the total number of solvents that now require testing has increased, a company is only required to test for those solvents which are likely to be present in the drug formulation. Since the solvents used in process development at each company are likely to be different, a company should consider developing a chromatographic testing system that addresses their specific needs.

In general, the strategy should be to develop a general testing method for residual solvents that:

- Resolves all solvents of interest likely to be present in their drug substances, excipients, and/or products
- Reduces analysis time for maximum sample throughput
- Obtains high accuracy and precision independent of the matrix
- Detects compounds at or below their control limits
- Provides qualitative and quantitative data that is consistent with USP/PhEur testing requirements

To determine the solvents that will be relevant to your company, you must interview your scientists involved in process development and any vendors for excipients and/or drug substance which are included in your formulation. Once this list has been compiled, compare it to the USP <467> list of solvents to determine what Class 1, 2, and 3 solvents are likely to be present. Based on your company's list of solvents, you can now design a strategy to accurately determine the level of residual solvents in your drug formulation.

Injection Techniques – Headspace vs. Direct Liquid

The main advantage of using headspace as an injection technique is that only the volatile portion of the sample is introduced into the column. Drug products often contain non-volatile components that can damage the GC column and cause problems with the analysis. However, there are certain Class 2 solvents that are not detected via headspace injection.[4] Depending on the solvents a company uses for manufacturing of a drug formulation, liquid injections might be necessary.

Class 2 solvents not detected via headspace injection

- Formamide
- 2-Ethoxyethanol
- 2-Methoxyethanol
- Ethylene glycol
- N-methylpyrrolidone
- Sulfolane

Direct Liquid Injection

There are three forms of direct liquid injection: split, splitless, and on-column. Both splitless and on-column injection techniques transfer the entire injected sample onto the column. These techniques

provide high sensitivity, but are not recommended when working with dirty samples because all of the contaminants will be transferred onto the column as well.

In a split injection, only a portion of the sample is injected onto the column while a majority of the sample is vented to waste. Split injection techniques significantly reduce the amount of contamination that enters the column and decreases the residence time of the sample in the injection port. The split ratio should be adjusted to reduce the amount of contamination that is injected onto the column while still achieving the required sensitivity limits. Typical split ratios are from 10:1 up to 100:1. Using higher split ratios will significantly prolong column life.

In a liquid injection, a relatively small sample amount is introduced (1-4 µL) into a heated injection port where it is instantaneously vaporized. The resulting volume of gas is referred to as the expansion volume and it is unique for each solvent. The volume of the sample should not exceed the volume of the GC liner because this can cause reproducibility problems.

For example, compare the expansions volume of a 1 µL injection of water vs. DMSO at 250 °C. A 1 µL injection of water will expand to about 1,100 µL of gas, whereas the DMSO will expand to only 300 µL. A typical 4 mm ID liner has a volume of about 900 µL, so the water injection would have exceeded the liner volume and caused problems with method precision.

Headspace Injection
To remain consistent with <467> methodology, headspace injection should be used whenever possible. Samples should be prepared in either a water or organic solution. Since many of the regulated solvents and drug components are more soluble in an organic solvent, an organic dilution solvent is usually recommended for the general method. An alternate procedure for sample preparation using water should be made available for use with samples that are not miscible in organic solvents. Heating may increase solubility for specific compounds.

The presence of impurities in organic solvents such as DMSO is well documented and can cause problems in chromatographic systems.[6] Alternate solvents such as DMI or DMA have fewer impurities, but do not always work as well for certain drug formulations. Similar problems are observed from commercially available water, even high grade HPLC water. Only water purified using well maintained filtering systems should be used for standard preparation. It is highly recommended to have a routine QC procedure in place to qualify incoming batches of solvent.

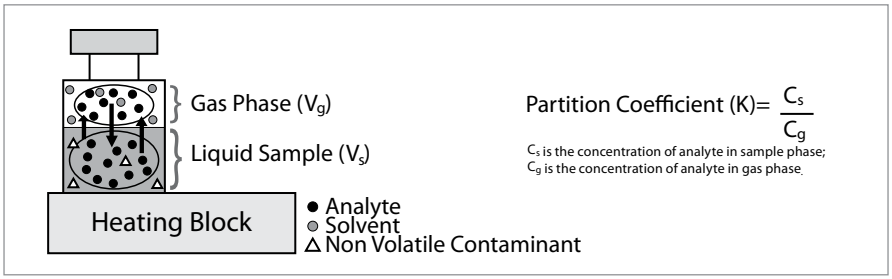

Figure 3: Headspace Sample Partition Coefficient (K)

When working with headspace injection techniques, the sample matrix can significantly affect the quantitative performance of the GC method. In a given matrix, each analyte will have a unique partition coefficient (K), which is an equilibrium distribution of the analyte between the liquid phase and the gas phase (Figure 3).

Sensitivity is largely affected by the concentration of the analyte in the gas phase. To achieve the detection limits required by <467>, it is important to drive as much analyte out of solution into the headspace as possible. There are several common strategies that can be employed to achieve this result: (1) increase the vial temperature, (2) increase the equilibration time, and/or (3) add matrix modifiers (salts) to increase the ionic strength of the solvent.

Experimental evidence has shown that increasing the temperature of the headspace vial above a certain level does not significantly increase the amount of analyte in the gas phase (Figures 4 and 5). The same is also true for the equilibration time, time points longer than 30 minutes are not necessary for many of the Class 1 and 2 solvents. The ionic strength of the sample does affect the equilibrium of many compounds. In order to improve reproducibility, it is recommended that all samples be supersaturated using an appropriate matrix modifier such as sodium chloride to eliminate sample variations.

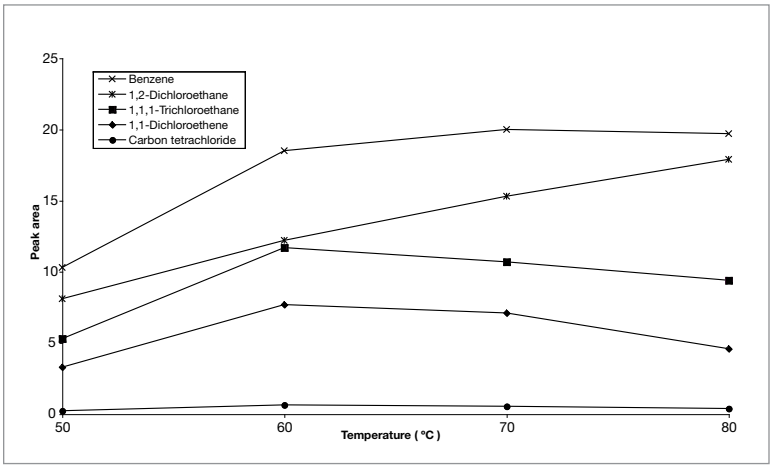

Figure 4. Static headspace peak area vs. vial temperature for class 1 volatiles

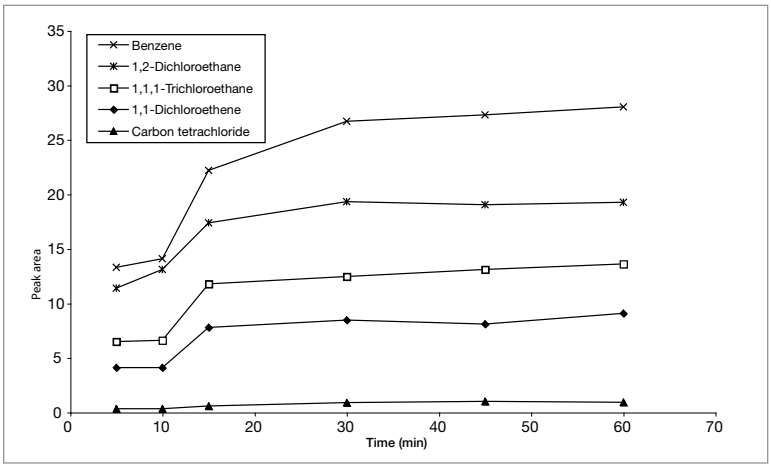

Figure 5. Static headspace response vs. vial exposure at 80 °C for class 1 volatiles

The addition of matrix modifiers is an effective way to decrease matrix variability. However, salts may not be compatible with organic solvents. In these cases, other analytical techniques must be explored in order to reduce matrix related sample variations.

In general, sample preparation has the largest affect on method performance. The USP Method specifies the use of their standards. However, good results have been obtained using in house prepared samples. Proper education and training regarding sample preparation are essential to achieving reproducible results.

The importance of consistent and effective sample preparation cannot be overstressed. Reproducibility in sample preparation will directly translate in to better reproducibility in method performance. An experienced analyst may prepare samples in less time resulting in less analyte evaporation and higher analyte recoveries. Long sample preparation times can result in misleading results because of excessive evaporation during the sample preparation steps.

3. Optimizing the GC Method

Following the conditions specified by the monograph, the total analysis time for all three samples would be > 3 hours. It is not feasible for most companies to spend 3 hours per sample to identify and quantitate 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.

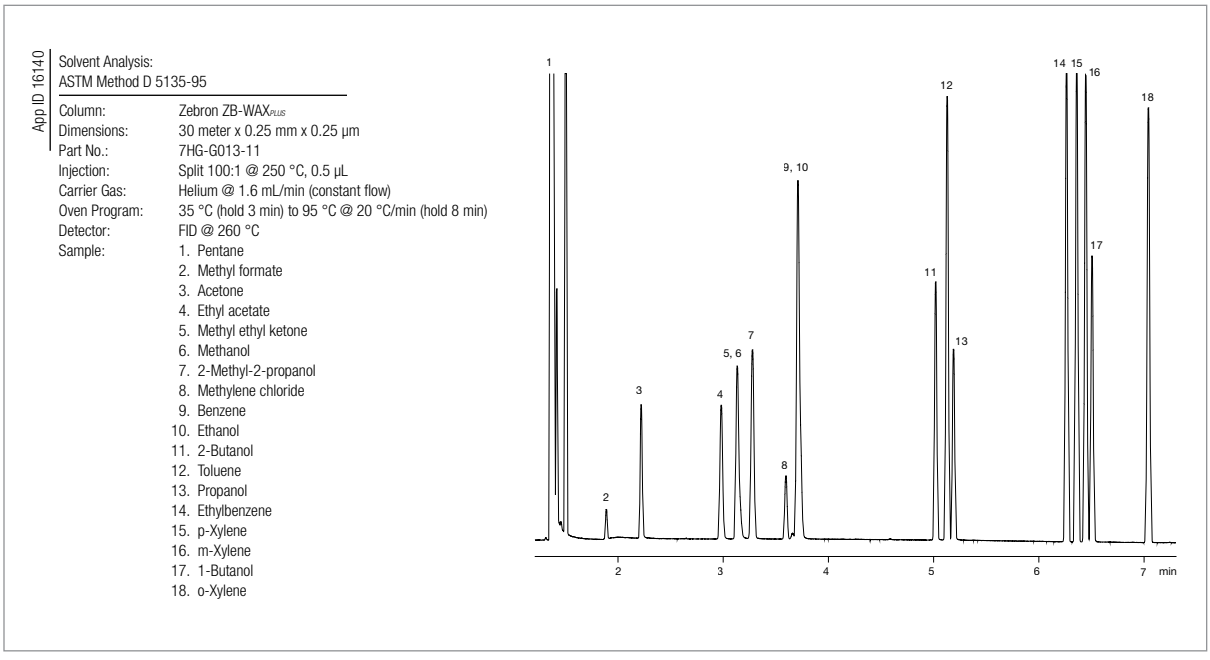

Figure 6. Separation of 18 solvents from Class 1, 2, & 3 using a G16 equivalent phase.

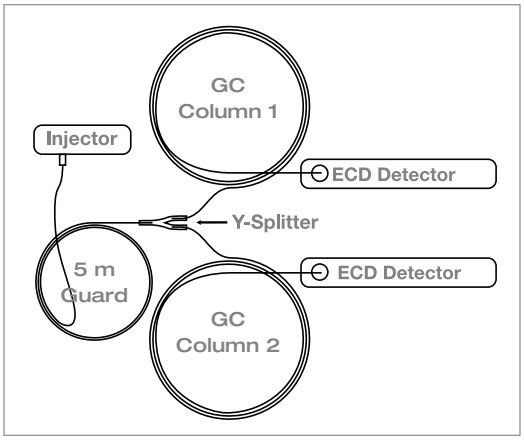

Figure 7. Diagram of dual column analysis.

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 6 shows the separation of 18 solvents from Class 1, 2, and 3 using a G16 (ZB-Wax$_{PLUS}$) 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 (ZB-624) equivalent 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 detector (FID) because it does not give any information about the identity of each peak. 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 (Figure 7).

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

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

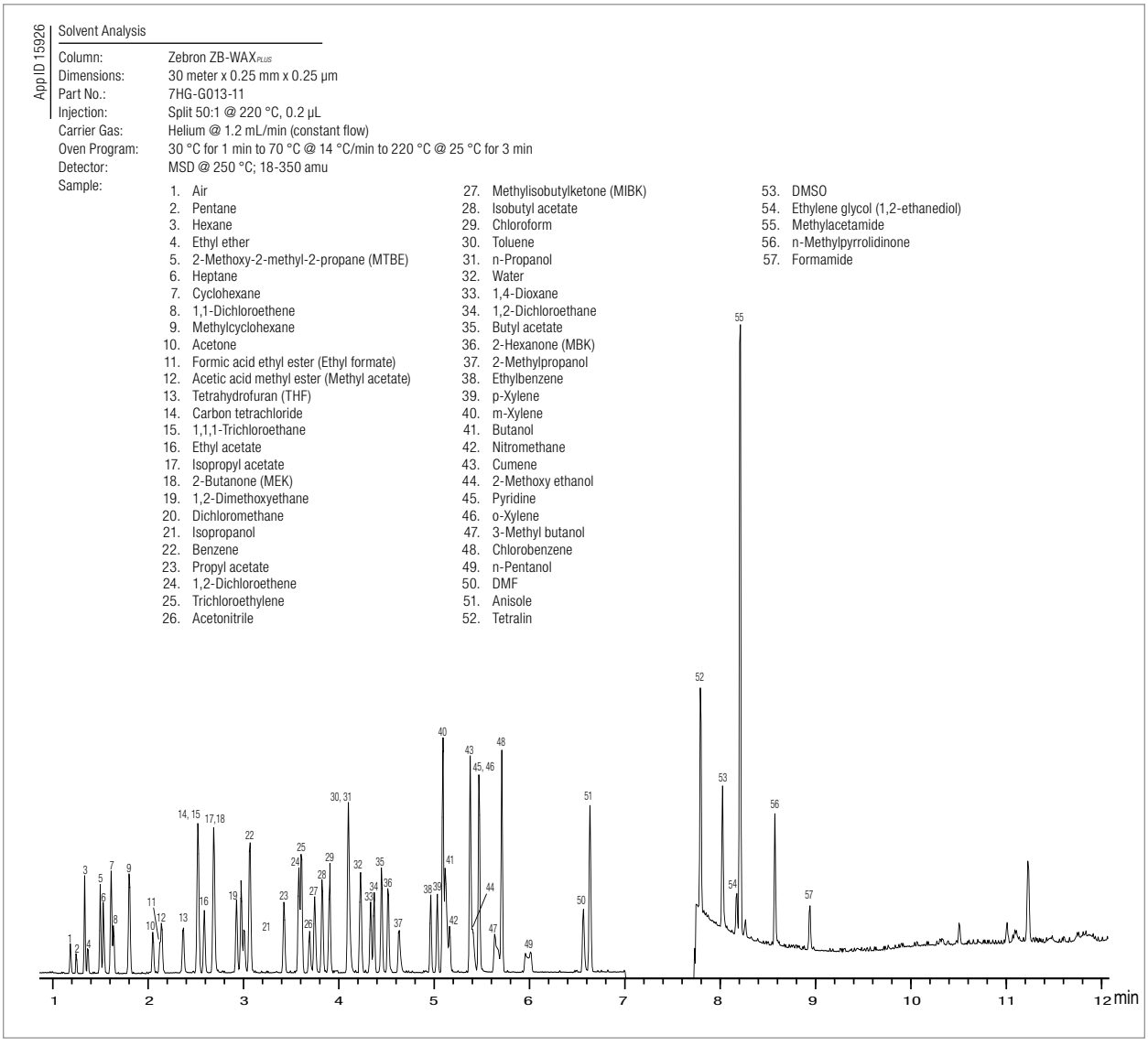

Figure 8. GC/MS analysis of class 1, 2, and 3 solvents.

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 the use of a single 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 for 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 8). 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.

Conclusion

The new USP regulations are aimed at improving consumer 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 company's 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 USP <467> monograph will not be official until July 2008, 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.

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Notes:

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