Residual Solvent Analysis with a Specifically Designed and Tested Agilent J&W DB-Select 624UI for USP <467> Column

Application Note

BioPharma

Author

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Abstract

This application note highlights the benefits of using a specifically designed and tested Agilent J&W DB-Select 624UI for USP <467>, 30 m × 0.32 mm, 1.8 µm column for USP residual solvent testing. Resolution of critical pairs, achieving acceptable signal-to-noise ratios, and pyridine peak shape are key chromatographic criteria for successful USP <467> residual solvent analysis. Example chromatograms for Class 1, 2A, and 2B standards on the new DB-Select 624UI <467> column are shown versus the results observed on less specifically designed and tested columns from other manufactures.

Introduction

Residual solvent testing of process intermediates, excipients, and formulated drug products provides an important safeguard to assure the safety of pharmaceutical products worldwide. Changes to United States Pharmacopeia (USP) General Chapter <467> Residual Solvents are closely aligned with International Committee on Harmonization (ICH) Q3C Guidelines for Residual Solvents [1,2]. Both groups have taken a toxicity/dosage-based approach to assess the level of risk that the presence of these solvents or organic volatile impurities (OVIs) present to the public. The analysis is typically conducted by static headspace with FID detection using a thick film G43-based stationary phase [3].

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Class 1 solvents are considered particularly hazardous and are to be avoided in pharmaceutical manufacturing. This class of solvents consists of known or suspected human carcinogens and environmental hazards. Target limits are in the low single digit mg/L range with the exception of 1,1,1-trichloroethane, which is considered an environmental hazard. There are several chromatographic challenges to be aware of when demonstrating Class 1 suitability at specified limits.
A signal-to-noise minimum of 3:1 is specified for each solvent in this class. This can be challenging for carbon tetrachloride at this level by FID detection. Another focal point to monitor is the critical pair resolution between benzene and 1,2-dichloroethane.

Class 2 solvents are considered less toxic, but their use is to be limited. Target limits for this class range from 50 to 3880 mg/L. In the 2A group of solvents, a resolution limit of not less than 1.0 is set for the resolution between acetonitrile and dichloromethane. 1,4-Dioxane detector response and resolution from methyl cyclohexane and pyridine peaks are key chromatographic aspects to track for successful analysis of the 2B group of solvents.

Class 3 solvents are considered less toxic and pose less risk to human health than either Class 1 or Class 2 solvents. An exposure limit of 50 mg per day or 5,000 mg/L is considered acceptable when justified for these materials. Some of these materials co-elute with other solvents on a G43 phase and may require follow up analysis by procedure B using a G16-based stationary phase. Example chromatograms and a peak retention table are available on our website for this class of solvents.

In these experiments, an Agilent J&W DB-Select 624UI for USP <467> column was used. The specific design and rigorous inertness testing of this new column help analysts consistently deliver results that meet or exceed the requirements of USP <467> residual solvent analysis. The DB-Select 624UI <467> is equivalent to the gas chromatography phase G43, as designated by the USP.

Materials and Methods

An Agilent Model 7890/5975C GC/MS System equipped with a Multi-Mode Inlet (MMI), an FID detector, an Agilent 7697A headspace sampler, and MSD Chem Station E.02.02 software was used for this series of experiments.

Chromatographic conditions for GC/Headspace analysis

Column:	Agilent J&W DB-Select 624UI for USP <467>, 30 m × 0.32 mm,1.8 µm (p/n 123-0334UI)
Carrier:	Helium, 2.2 mL/min constant flow at 40 °C
Oven:	40 °C (20 min), then 10 °C/min to 240 °C (5 min)
Inlet:	MMI, 140 °C, 1 µL split 5:1
Sample vol:	1.0 mL loop
Inlet liner:	1 mm straight single taper Ultra Inert liner (p/n 5190-4047)
FID:	250 °C, H_2 30 mL/min, air 400 mL/min, N_2 constant col + makeup = 30 mL/min

Flow path supplies

Vials:	20 mL Flat bottom crimp cap headspace vials (100 pk, p/n 5182-0837)
Vial caps:	Headspace crimp cap /high performance septa (100 pk, 5190-3987)
Crimper:	20 mm electronic crimper (p/n 5190-3189)
Transfer line:	0.53 mm deactivated fused silica (5 m, p/n 160-2535-5)
Fitting:	1/6 to 1/32 inch reducing fitting (p/n 0100-2594)
Septum:	Non-stick, Bleed and Temperature Optimized (50 pk, p/n 5183-4757)
Inlet liner:	1 mm straight single taper Ultra Inert liner (p/n 5190-4047)
Gold seal:	Gold plated inlet seal with washer (10/pk, p/n 5190-2209)
Ferrules:	0.5 mm id short 85/15 Vespel/graphite (10 pk, p/n 5062-3514)
Magnifier:	20x Magnifier loop (p/n 430-1020)

Standards

Class 1:	USP 467 Class 1 (p/n 5190-0490)
Class 2A:	USP 467 Class 2A (p/n 5190-0492)
Class 2B:	USP 467 Class 2B (p/n 5190-0513)

Standard preparation

USP Class 1, Class 2A, and Class 2B standards were prepared as outlined in Figure 1, in accordance with USP General Chapter <467> methodology. Dimethyl sulfoxide (99.5%) was purchased from Sigma Aldrich, St Louis, MO 63101 USA. De-ionized water was from an in-laboratory water purification system.

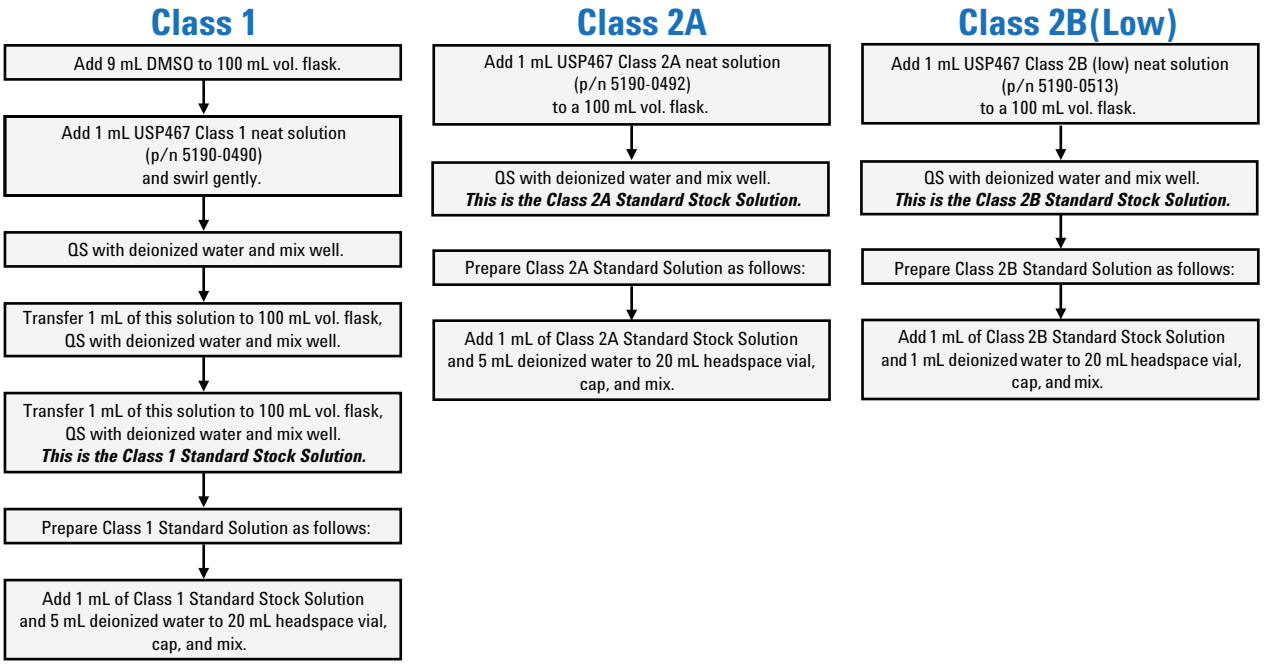

Figure 1. USP 467 standard preparation procedure A for water-soluble articles.

Results and Discussion

Column performance for Class 1 standards

Meeting the signal-to-noise requirement of not less than 3:1 for carbon tetrachloride can be challenging at specific limits of detection by FID. Another key chromatographic element to monitor closely is the separation between benzene and 1,2-dichloroethane. Figure 2 shows a headspace injection of a Class 1 standard on a DB-Select 624UI <467> capillary column. Here, the carbon tetrachloride signal-to-noise value was 6.85, and the resolution (Rs) between benzene and 1,2-dichoroethane was 1.82.

In Figure 3, expanded views of critical sections of Class 1 standard injections are shown to illustrate that G43 columns from other manufacturers are not all created equal. Each of these columns was tested on the same instrument under the same conditions with the same dimension columns. One vendor's column did not meet the signal-to-noise acceptance criteria for carbon tetrachloride.

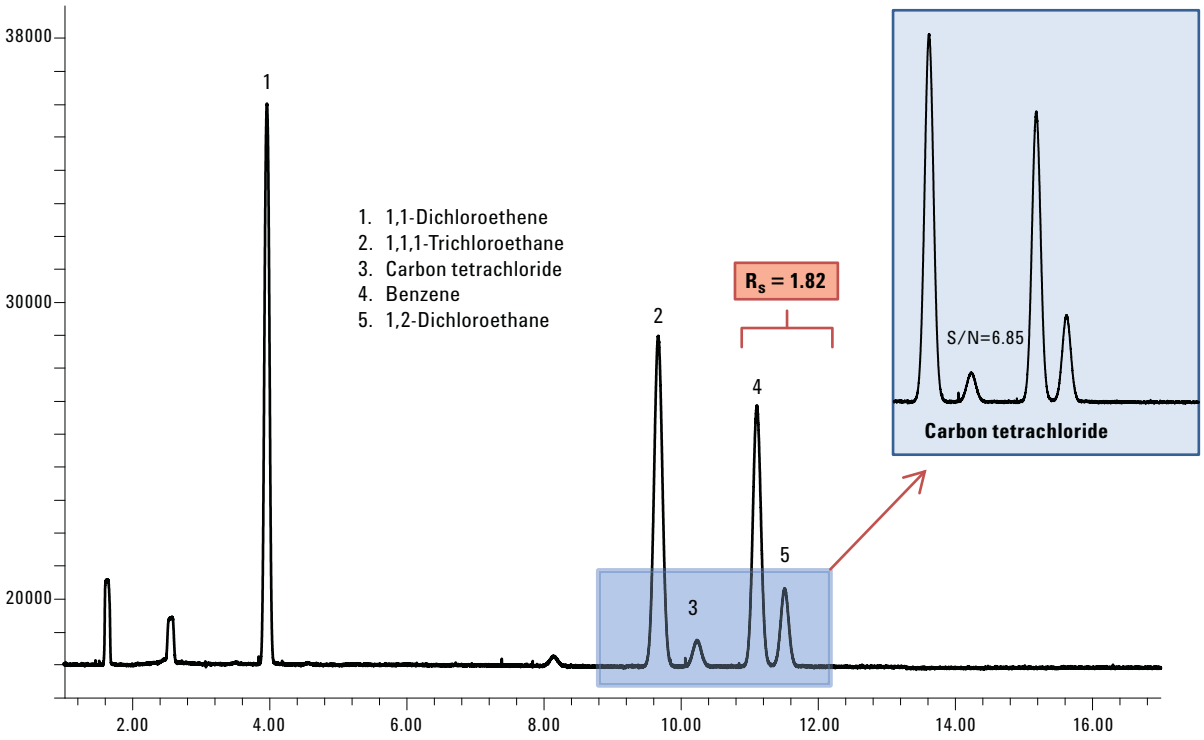

Figure 2. FID trace of Class1 solvent standard at USP< 467> specified limits on an Agilent J&W DB-Select 624UI for USP <467>, 30 m x 0.32 mm, 1.8 µm column (p/n 123-0334UI).

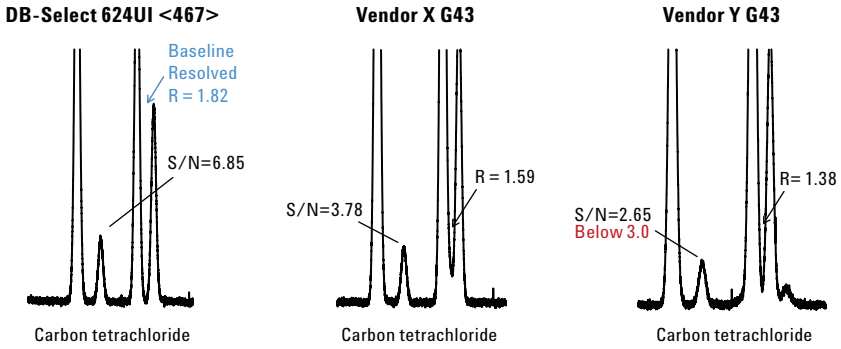

Figure 3. Benzene/1,2-dichloroethane critical pair separation and carbon tetrachloride signal-to-noise comparison between Agilent J&W DB-Select 624UI for USP <467> column and G43 phase columns from other manufactures. Note the column from vendor Y failed to meet signal-to-noise criteria for carbon tetrachloride.

Column performance for Class 2A standards

Resolution of the acetonitrile/dichloromethane critical pair is specified to be no less than 1.0. Figure 4 shows a resolution of 2.13 for this critical pair on the DB-Select 624UI <467> column. Another key chromatographic element to track in the Class 2A standard is the response of 1,4 dioxane at 380 mg/L and its resolution from methyl cyclohexane, which has a higher permissible limit of 3,880 mg/L.

Figure 5 compares the resolution of the acetonitrile/dichloromethane critical pair observed on the DB-Select 624UI <467> column with the G43 column offerings from 2 other vendors. Each of these columns was tested on the same instrument under the same conditions with the same dimension columns.

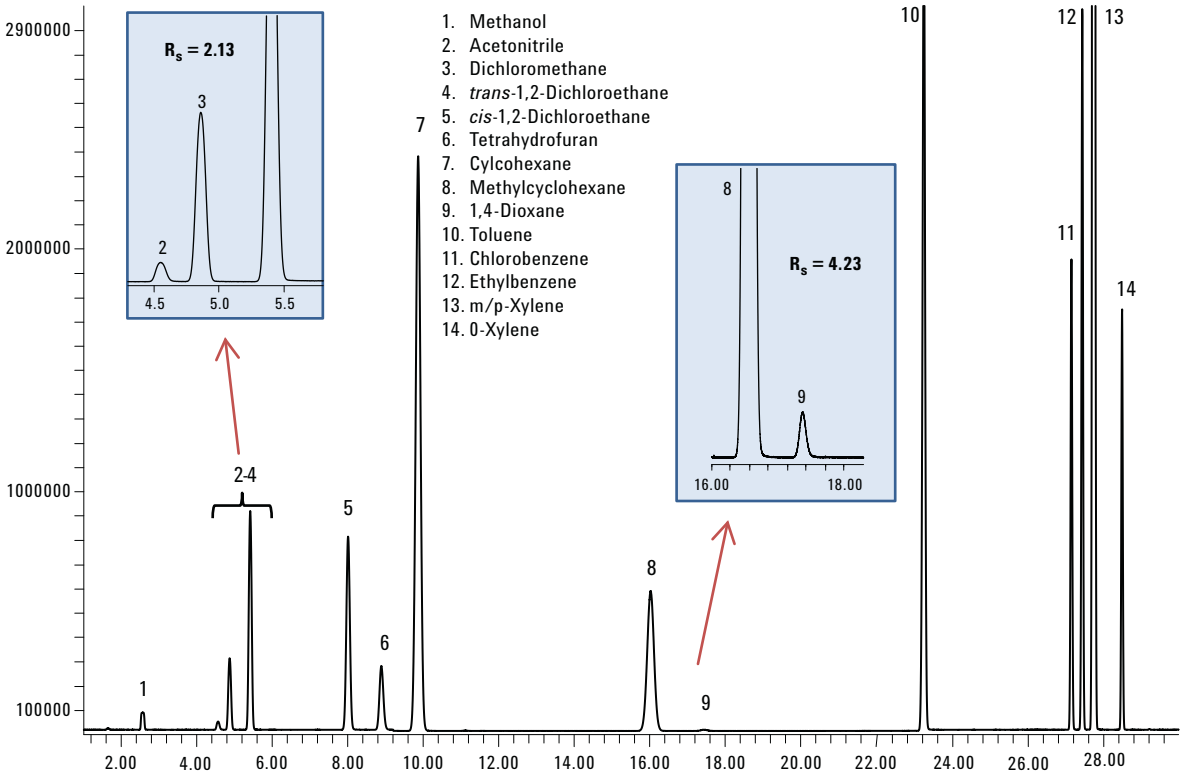

Figure 4. FID trace of Class 2A solvent standard at USP 467 specified limits on an Agilent J&W DB-Select 624UI for USP <467>, 30 m × 0.32 mm, 1.8 µm column (p/n 123-0334UI).

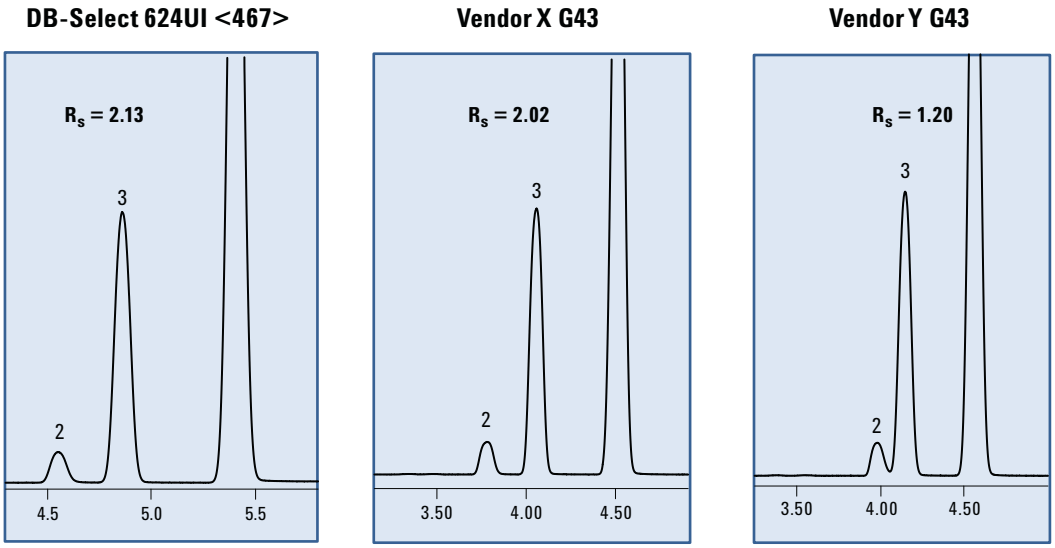

Figure 5. Acetonitrile/dichloromethane critical pair separation comparison between the Agilent J&W DB-Select 624UI for USP <467> column and G43 columns from other manufactures.

Column performance for Class 2B standards

Pyridine peak shape or degree of tailing is an important performance parameter to monitor in the Class 2 B standard solution. In Figure 6, the USP tailing value for pyridine was 1.3 on the DB-Select 624UI <467> column.

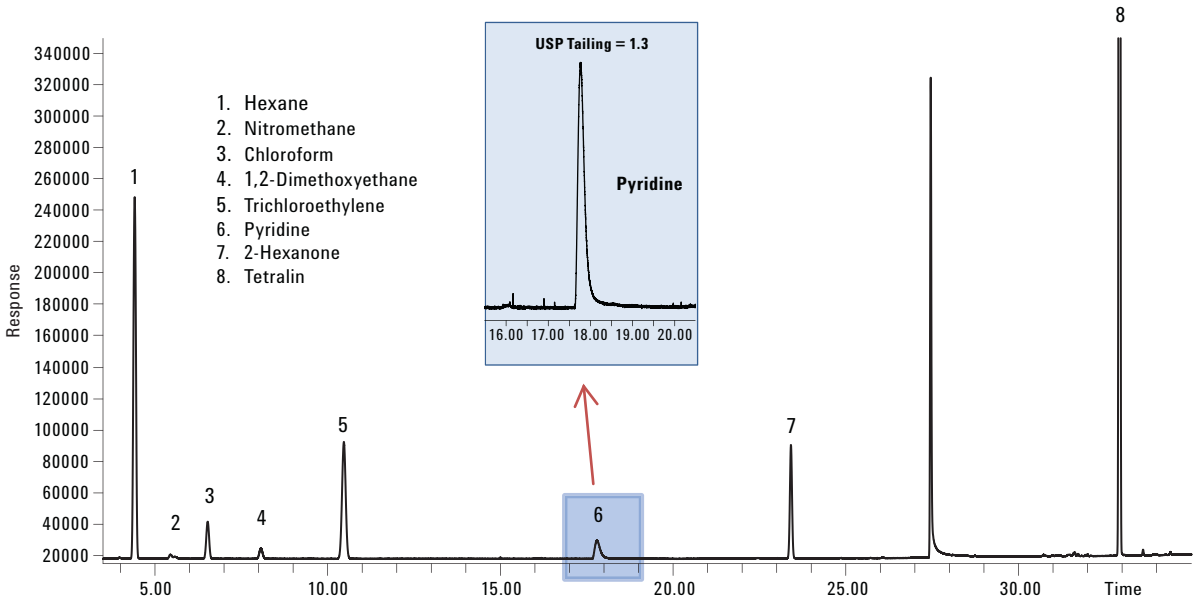

Figure 6. FID trace of Class 2B solvent standard at USP <467> specified limits on an Agilent J&W DB-Select 624UI for USP <467>, 30 m × 0.32 mm, 1.8 µm column (p/n 123-0334UI).

Figure 7 compares the USP tailing results for pyridine seen on the Agilent column with the results obtained on 2 G43 columns from other vendors. Each of these columns was tested on the same instrument under the same conditions with the same dimension columns. Note that no pyridine was detected at the 200 mg/L level on Vendor P's column.

Conclusions

The Agilent J&W DB-Select 624UI for USP <467> column demonstrates excellent chromatographic performance for the Class 1, Class 2A, and Class 2B at USP <467> specified limits. Critical pairs were resolved, and signal-to-noise values greater than 6 were observed for carbon tetrachloride at the specified limit. The USP tailing factor for basic pyridine was 1.3, significantly better than the other G43 phases tested under the same conditions.

Indications are that this column delivers superior performance in comparison to less specifically designed and tested G43 phases. Inertness testing makes the difference, and once again, innovations from Agilent Technologies help analysts meet their continuing needs for good separations.

References

1. United States Pharmacopeia. USP 34-NF29, General Chapter USP <467> Residual Solvents. USP, Pharmacopeia Convention Inc., Rockville MD, USA (12/2011).
2. International Conference on Harmonization. Impurities: Guideline for Residual Solvents, Q3C(R5). ICH of Technical Requirements for Registration of Pharmaceuticals for Human Use, Current Step 4 Version (2/2011).
3. Roger L. Firor. Analysis of USP <467> Residual Solvents with Improved Repeatability Using the Agilent 7697A Headspace Sampler. Agilent Technologies, Inc., Publication number 5990-7625EN (2011).

For More Information

These data represent typical results. For more information on our products and services, visit our Web site at www.agilent.com/chem/624UI.

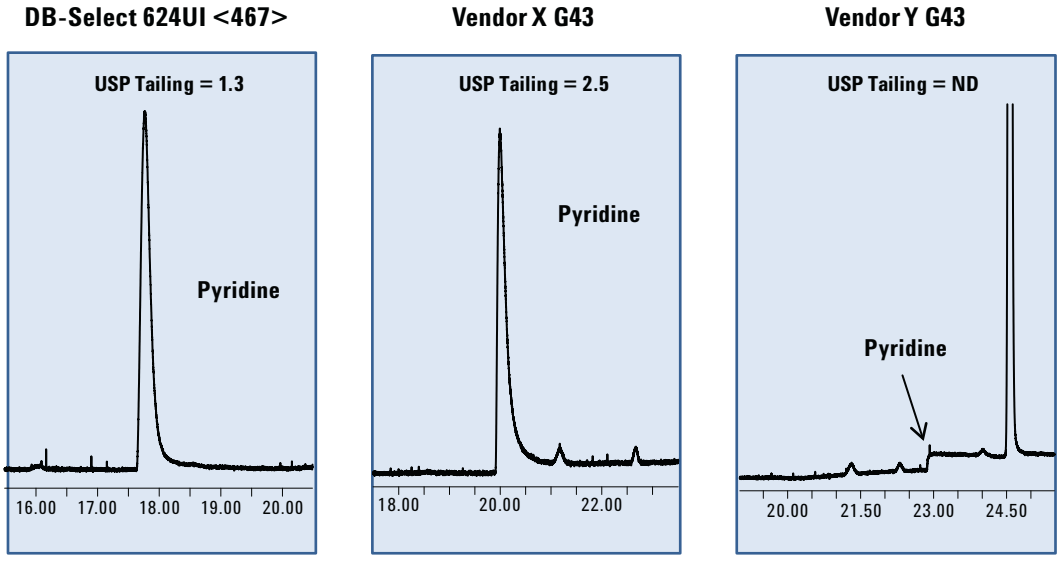

Figure 7. Pyridine peak shape comparison at 200 mg/L between the Agilent J&W DB-Select 624UI for USP <467> column and G43 columns from other manufactures.

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