Residual Solvents Analysis Based on the 2025 USP <467> and Chinese Pharmacopoeia (ChP 0861)

Using the Agilent 8697 headspace sampler and Agilent 8890B GC system

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Abstract

Regulatory requirements for residual solvents change over time. The United States Pharmacopeia (USP) <467> released new guidance in September 2025, expanding the list and performance requirements within class 2B solvents. In the same year, the Chinese Pharmacopoeia (ChP) was also revised, including an update to General Chapter 0861 (0861). This application note describes the determination of class 1 and 2 residual solvents at their specified limit levels in accordance with the current USP <467>. The same analytical workflow is also aligned with the general principles and analytical requirements described in ChP 0861. An Agilent 8697 headspace sampler combined with a dual-column, dual-flame ionization detection (FID) gas chromatograph (GC) configuration was applied to enable efficient screening and confirmation on complementary stationary phases. The method delivered consistent chromatographic performance with suitable resolution, peak shape, and repeatability. Both helium and nitrogen were evaluated as carrier gases, and the results met or exceeded the acceptance criteria defined in both USP <467> and ChP 0861. In addition to analytical performance, the intelligent features of the Agilent 8890B GC system improve operational reliability and simplify routine use, with GC Assist providing guided, step-by-step support for efficient troubleshooting.

Introduction

Residual solvents are routinely introduced during pharmaceutical manufacturing as part of synthesis, purification, or formulation processes. Because these volatile organic compounds may pose toxicological risks, their levels must be carefully monitored to ensure patient safety and regulatory compliance. As a result, residual solvent analysis remains a critical component of quality control throughout the pharmaceutical development and manufacturing lifecycle.

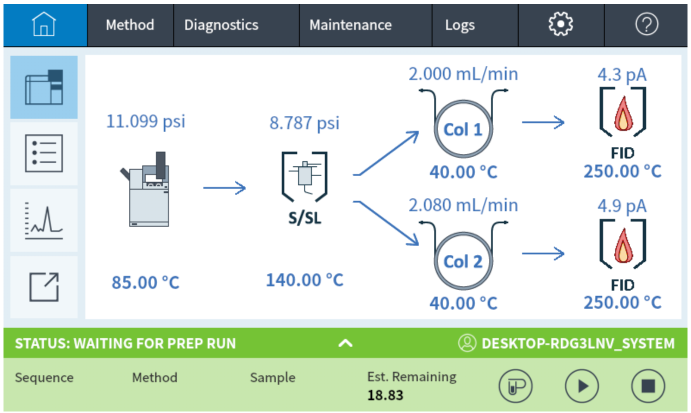
USP <467> provides a harmonized framework for residual solvent analysis, defining solvent classifications, concentration limits, and analytical requirements.[1] In September 2025, USP <467> was revised to reflect updated toxicological evaluations and regulatory expectations. The revised chapter expanded the class 2B solvent list and introduced performance requirements for newly added compounds, including tertiary butyl alcohol and cyclopentyl methyl ether (CPME). These updates increase the analytical scope of residual solvent testing and place greater emphasis on consistent system performance and suitability verification. In China, residual solvent control is governed by General Chapter 0861 of the Chinese Pharmacopoeia (ChP 0861)[2], which adopts a risk based classification system consistent with the International Council for Harmonisation (ICH) Q3C.[3] Although the Chinese Pharmacopoeia uses different terminology for analytical procedures, its regulatory intent, solvent classification, and control principles are harmonized with USP <467>.

Gas chromatography with headspace sampling is widely used for residual solvent determination due to its robustness and suitability for volatile analytes. Alongside evolving regulatory requirements, modern GC systems have increasingly focused on intelligent operation to support method execution and compliance. The Agilent 8890B gas chromatograph incorporates GC Assist to help users perform a performance check of the GC system. When performance criteria are not met, the GC system provides alerts to notify the user. Upon user instruction, the GC can initiate a guided troubleshooting workflow, supporting step-by-step fault diagnosis through autonomous diagnostic functions, helping both experienced and less experienced analysts resolve issues efficiently during routine operation.

In this application note, a headspace GC/FID method is presented for the determination of class 1, 2A, and the expanded class 2B residual solvents. This study demonstrates how updated regulatory requirements can be addressed using an intelligent GC platform that supports reliable system performance assessment, simplified troubleshooting, and consistent analytical performance.

Experimental

The experimental conditions described in this study follow the general chromatographic principles outlined in USP <467> procedures A and B. They are also consistent with the recommended headspace GC methods described in ChP 0861. In this work, the screening and confirmation concepts of procedures A and B were implemented simultaneously through a dual-column, dual-FID/GC configuration. Samples were introduced by an Agilent 8697 headspace sampler to an 8890B GC and equally split to an Agilent DB-Select 624 UI and a DB-WAX UI column for parallel detection, as shown in Figure 1. Comparable chromatographic performance was achieved with both helium and nitrogen carrier gases. Data were acquired using Agilent OpenLab CDS version 2.8, and noise was determined using a peak-to-peak (PtoP) approach for calculation of signal-to-noise ratios for target analytes.



STATUS: WAITING FOR PREP RUN

Est. Remaining 18.83

Figure 1. Dual-column, dual-FID GC system for residual solvents analysis. A 0.5 m × 0.32 mm id fused silica tubing was connected from the inlet to an unpurged two-way splitter to split the injected components equally between the two columns.

Table 1. Gas chromatography conditions.

Parameter	Value
Agilent 8697 Headspace Sampler	
Vial Pressurization Gas	N_2
Loop Size	1 mL
Vial Size	20 mL
Vial Shaking	8 (188 shakes/min)
Vial Equilibration Time	40 min
Inject Time	0.5 min
Oven Temperature	85 °C
Loop Temperature	85 °C
Transfer Line	0.53 mm id, deactivated fused silica (p/n 160-2535-5)
Transfer Line Temperature	100 °C
Vial Fill Pressure	15 psi
Loop Fill Mode	Custom
Loop Ramp Rate	40 psi/min
Loop Final Pressure	4 psi
Agilent 8890B GC	
Parameter	Value
Inlet	SSL, 140 °C, split ratio 10:1
Liner	Ultra inert, straight, 1 mm id (p/n 5190-4047)
CFT Device	Unpurged two-way splitter (p/n G3181B)
Column	**Column 1:** Agilent DB-Select 624 UI, 30 m × 0.32 mm, 1.8 µm (p/n 123-0334UI) **Column 2:** Agilent DB-WAX UI, 30 m × 0.32 mm, 0.25 µm (p/n 123-7032UI)
Carrier	He and N_2 carrier gas 2 mL/min, constant flow
Tubing	0.32 mm id, deactivated fused silica tubing (p/n 160-2325-5)
Oven	Helium carrier gas: 40 °C (5.5 min), then 15 °C/min to 180 °C, hold 2.5 min Nitrogen carrier gas: 38 °C (5.5 min), then 15 °C/min to 180 °C, hold 4 min
FID (Both Channels)	Temperature: 250 °C, hydrogen: 30 mL/min, air: 300 mL/min,
Data Rate	10 Hz

Chemicals and standards

The standards used in this study:

Class 1: Residual solvent 467 class 1 (part number 5190-0490)

Class 2A: Residual solvent 467 class 2A (part number 5190-0492)

Class 2B: Residual solvent 467 class 2B (USP part number 1601292), purchased from Alta Scientific Co. Ltd.

The single standards of methyl isobutyl ketone (MIBK) and cumene were purchased from Alta Scientific Co. Ltd.

Class 1 solvents

- 1 mL stock solution vial plus 9 mL of DMSO, diluted to 100 mL with water
- 1 mL from step 1, diluted to 100 mL with water
- 10 mL from step 2, diluted to 100 mL with water
- 1 mL from step 3 plus 5 mL of water in a 20 mL headspace vial

Class 2A solvents

- 1 mL stock solution vial, spiked with MIBK and cumene, then diluted to 100 mL with water
- 1 mL from step 1 plus 5 mL of water in a 20 mL headspace vial

Class 2B solvents

- 1 mL stock solution vial, diluted to 100 mL with water
- 5 mL from step 1 plus 1 mL of water in a 20 mL headspace vial

Results and discussion

As all class 1, 2A, and 2B solvents were prepared at their USP <467> limit concentrations, several compounds exhibited relatively low detector response, including carbon tetrachloride, 1,4-dioxane, 1,2-dimethoxyethane, and nitromethane. In addition, acetonitrile and pyridine showed both low response and peak tailing on the DB-Select 624 UI column, making peak integration sensitive to baseline definition; therefore, careful optimization of integration parameters is recommended.

USP <467> specifies mandatory system suitability requirements for residual solvent analysis, which are summarized in Table 2. These include minimum signal-to-noise ratio requirements for class 1 solvents and minimum resolution requirements for critical class 2A solvent pairs in both procedures A and B. Compliance with these criteria ensures reliable quantitative performance for routine residual solvent analysis.

In comparison, ChP 0861 defines system suitability requirements in a more flexible way. Instead of setting fixed limits for specific solvents, it allows appropriate performance criteria to be established based on method validation and actual analytical needs. Although the two pharmacopeias differ in how detailed these requirements are, USP <467> and ChP 0861 ultimately aim to ensure adequate sensitivity and chromatographic performance for reliable residual solvent analysis.

Table 2. USP <467> system suitability requirements for residual solvent analysis.

Procedure	Solvent Class	Compound Name	Requirement by USP <467>
A	Class 1	S/N (1,1,1 trichloroethane)	≥ 5
	Class 1	S/N (other solvents)	≥ 3
	Class 2A	Resolution (acetonitrile/ methylene chloride)	≥ 1
B	Class 1	S/N (benzene)	≥ 5
	Class 1	S/N (other solvents)	≥ 3
	Class 2A	Resolution (MIBK/ *cis*-1,2-dichloroethene)	≥ 1
	Class 2B	Resolution (1,2-dimethoxyethane and cyclopentyl methyl ether)	≥ 1.5

Figures 2 to 7 illustrate the analysis of class 1, 2A, and 2B residual solvent mixtures on DB-Select 624 UI and DB-WAX UI columns using helium and nitrogen carrier gases. For class 1 solvents analyzed under procedure A, when helium was used as the carrier gas, the signal-to-noise ratios (S/N) for 1,1,1-trichloroethane and carbon tetrachloride were 78.3 and 11.1, respectively, while with nitrogen carrier gas, the corresponding S/N values were 67.8 and 9.6. In procedure B for class 1 solvents, benzene exhibited similarly high S/N values with both carrier gases, reaching 105.1 with helium and 104.8 with nitrogen. For class 2A solvents analyzed under procedure A, the resolution between acetonitrile and methylene chloride was 3.4 for both helium and nitrogen carrier gases, demonstrating equivalent chromatographic performance. In procedure B, adequate separation was achieved for both class 2A and 2B solvents. The resolution between acetonitrile and MIBK (class 2A) was 1.9 with helium carrier and 1.4 with nitrogen carrier, meeting the USP <467> acceptance criterion. For class 2B solvents, 1,2-dimethoxyethane and cyclopentyl methyl ether were well resolved, with resolutions of 3.7 and 3.4 under helium and nitrogen carrier gas conditions, respectively.

In the newly released 2025 edition of USP <467>, tertiary butyl alcohol and cyclopentyl methyl ether (CPME) have been added to the list of class 2B solvents. On the DB Select 624 UI column operated under procedure A, pyridine elutes immediately after CPME. The CPME peak is relatively large, whereas pyridine appears as a smaller peak, and both compounds exhibit some degree of peak tailing. Despite these challenges, baseline separation between CPME and pyridine was successfully achieved. On the DB WAX UI column operated under procedure B, CPME eluted at 3.91 minutes, while pyridine eluted at 9.14 minutes (as shown in Figure 6). The two peaks were completely resolved with no interference, and both compounds exhibited more symmetrical peak shapes. Furthermore, for class 2B solvents, no coelutions were observed in either procedure A or B, regardless of whether helium or nitrogen was used as the carrier gas, fully meeting the chromatographic requirements of USP <467>.

To evaluate the overall system stability, helium and nitrogen were separately used as carrier gases for nine consecutive injections of class 1, 2A, and 2B solvent mixtures. Peak area repeatability was assessed for all analytes, and the results are summarized in Table 3 and Figure 8. When helium was used as the carrier gas under both procedure A and B conditions, the average percent relative standard deviation (%RSD) of peak areas across all analytes was 1.32%, with 47% of the compounds showing peak area RSDs below 1%. Using nitrogen as the carrier gas, the average peak area %RSD for all analytes was 1.28%, and 50% of the compounds exhibited peak area RSDs below 1%. These results demonstrate that the repeatability obtained with nitrogen carrier gas is comparable to that obtained with helium, indicating consistent and robust system performance regardless of carrier gas choice.

Table 3 also summarizes the retention time (RT) repeatability for each residual solvent on two capillary columns using helium and nitrogen as carrier gases. Overall, the DB-Select 624 UI column demonstrated better RT repeatability under both carrier gas conditions, with average RT RSD values of approximately 0.009%. Slightly higher RT variability was observed for the DB-WAX UI column, where the average RT RSD was around 0.018% under helium and nitrogen carrier gas. The 6 mL standard solution in a headspace vial contained a high proportion of water, and a large amount of water evaporated into the vial headspace during vial equilibration in the oven and was subsequently introduced into the GC column together with the analytes. The WAX stationary phase is relatively more sensitive to water, which can influence retention time stability. To further evaluate the impact of water on analyte retention on the DB-WAX UI column, the column was connected to a thermal conductivity detector (TCD) on another GC system. The water peak exhibited a baseline width greater than 1.5 minutes, with the end of the water peak eluting close to *m*-xylene. Compounds eluting within the water peak tail or after it—such as cumene, *o*-xylene, chlorobenzene, pyridine, and tetralin—were affected by water, resulting in slightly poorer RT repeatability. This effect explains why the average RT RSD values obtained on the DB-Select 624 UI column were consistently lower than those observed on the DB-WAX UI column.

Nevertheless, the observed retention time shifts were minimal and had no impact on qualitative identification. In fact, significant magnification of the chromatograms was required to visualize these small RT variations.

These results further demonstrate excellent retention time stability and overall performance of the Agilent GC columns, even under challenging, water-rich headspace conditions.

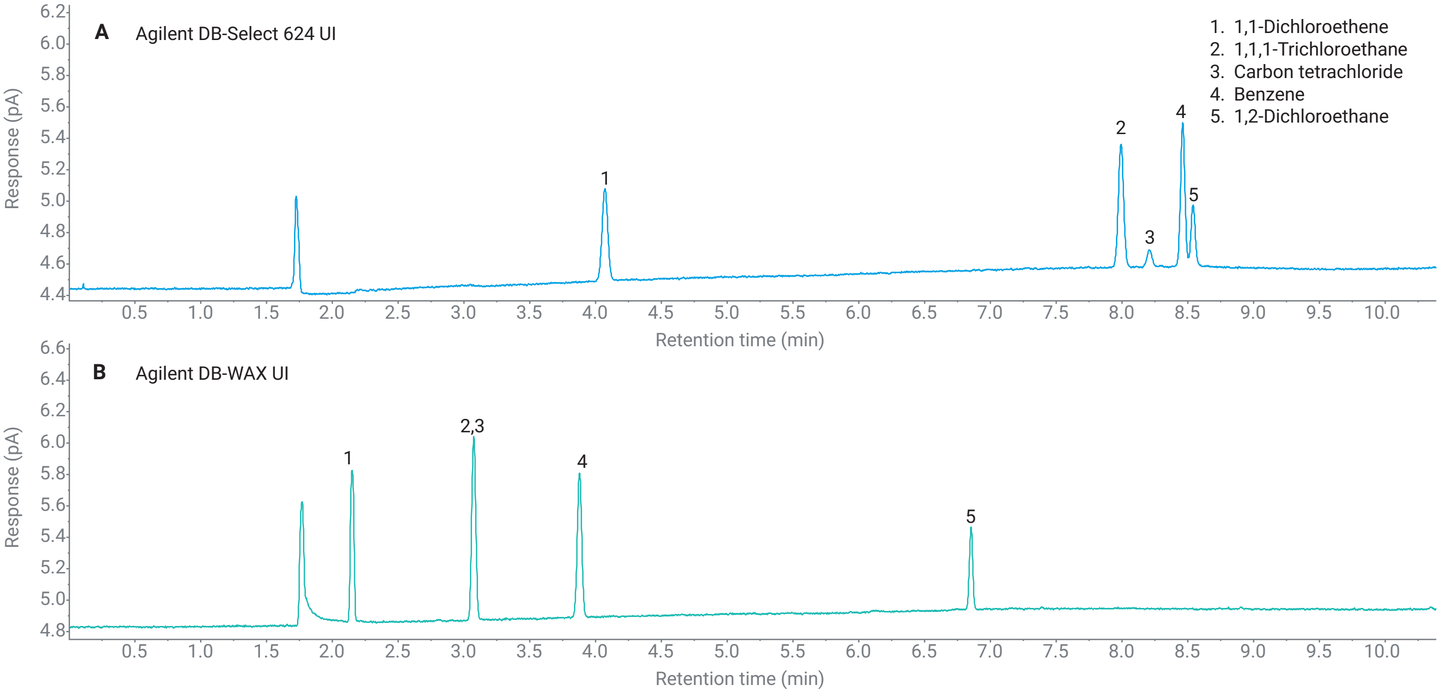


Figure 2. GC/FID chromatograms of class 1 standard solution on an Agilent DB-Select 624 UI column (procedure A) and an Agilent DB-WAX UI column (procedure B) using helium carrier gas.

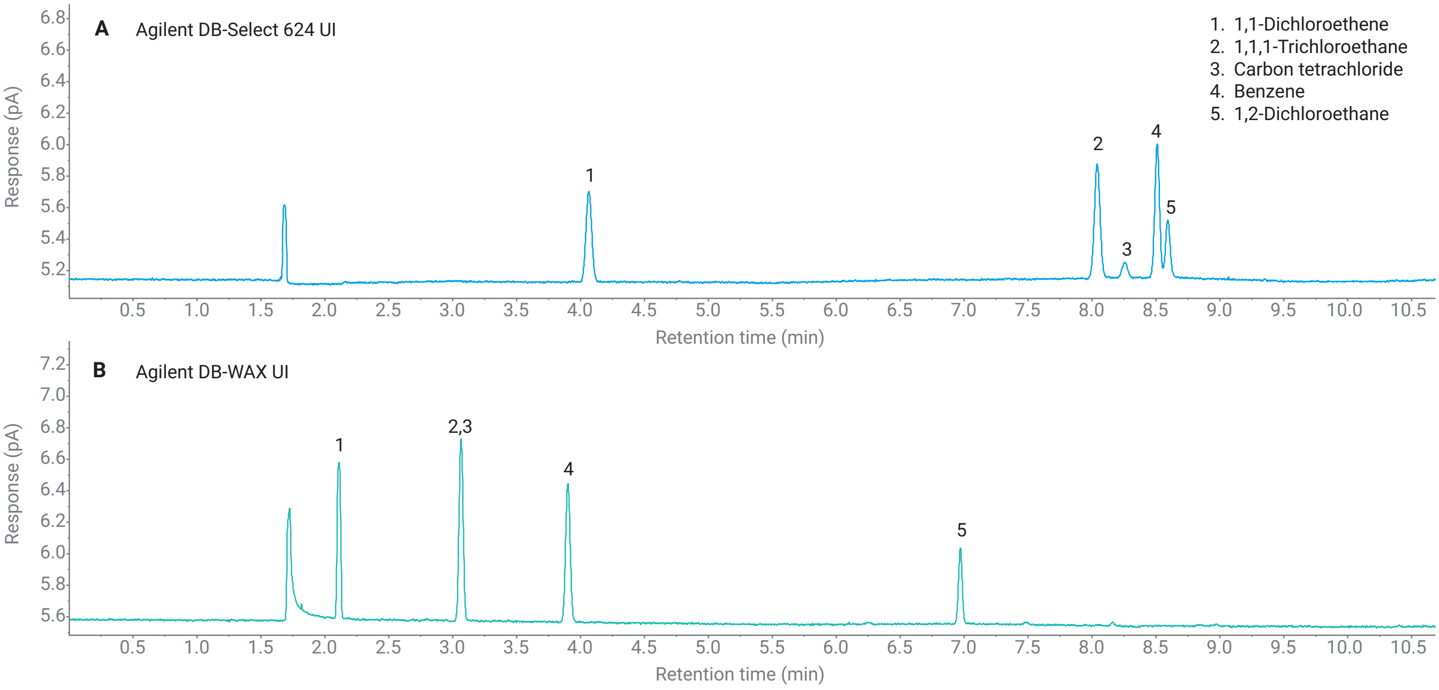


Figure 3. GC/FID chromatograms of class 1 standard solution on an Agilent DB-Select 624 UI column (procedure A) and an Agilent DB-WAX UI column (procedure B) using nitrogen carrier gas.

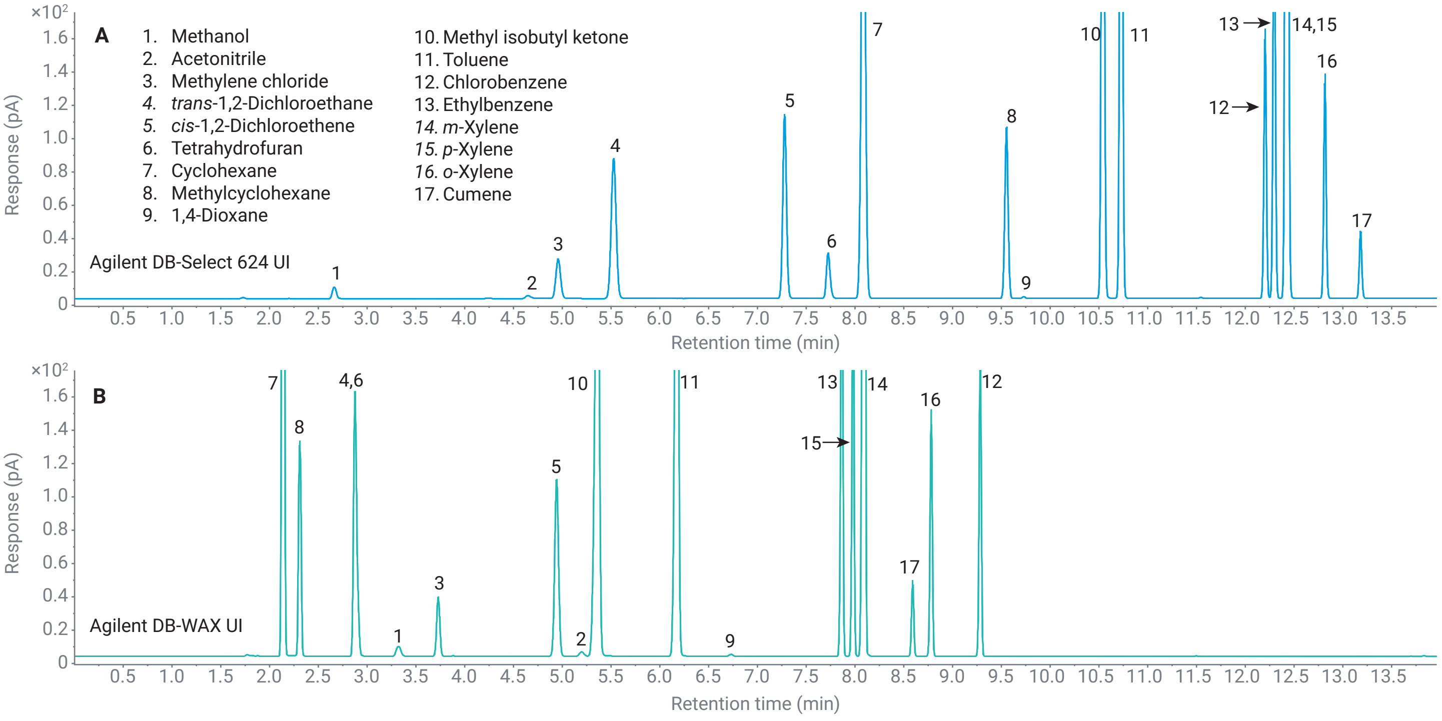


Figure 4. GC/FID chromatograms of class 2A standard solution on an Agilent DB-Select 624 UI column (procedure A) and an Agilent DB-WAX UI column (procedure B) using helium carrier gas.

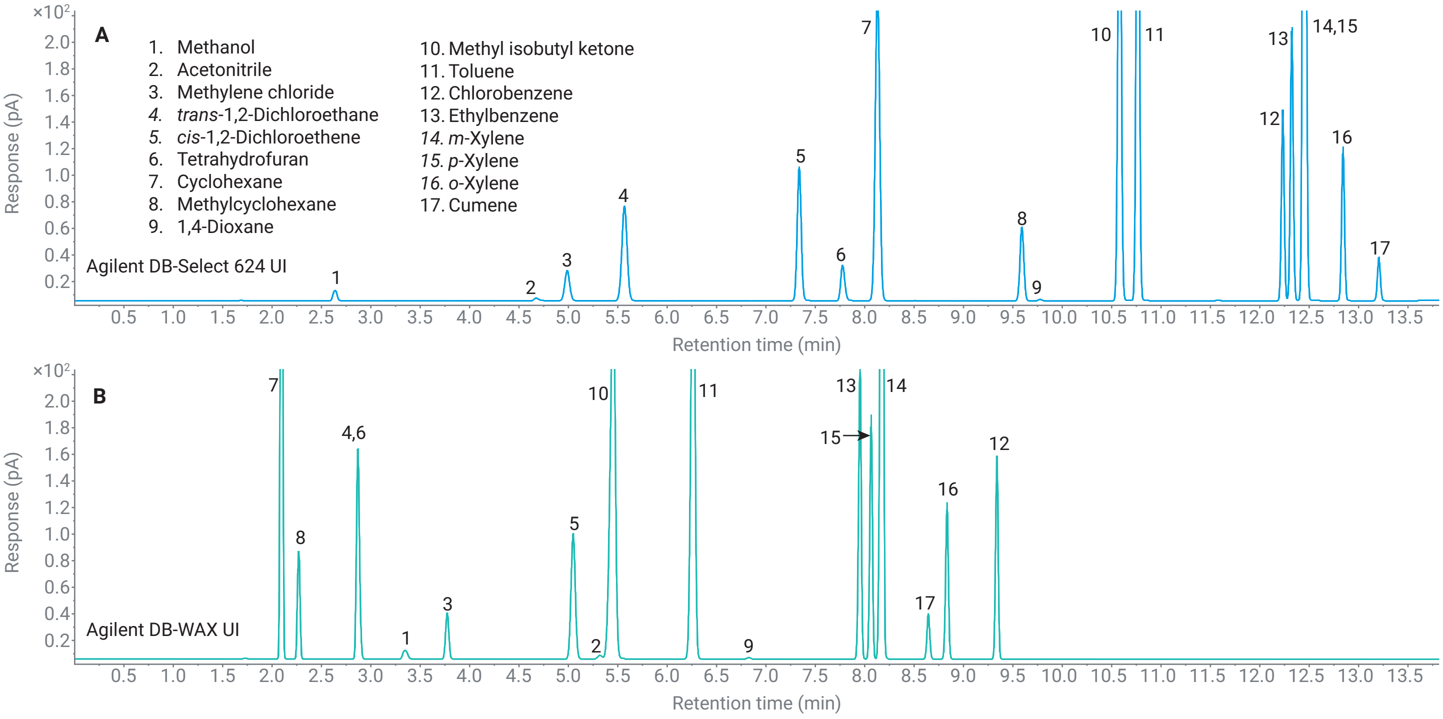


Figure 5. GC/FID chromatograms of class 2A standard solution on an Agilent DB-Select 624 UI column (procedure A) and an Agilent DB-WAX UI column (procedure B) using nitrogen carrier gas.

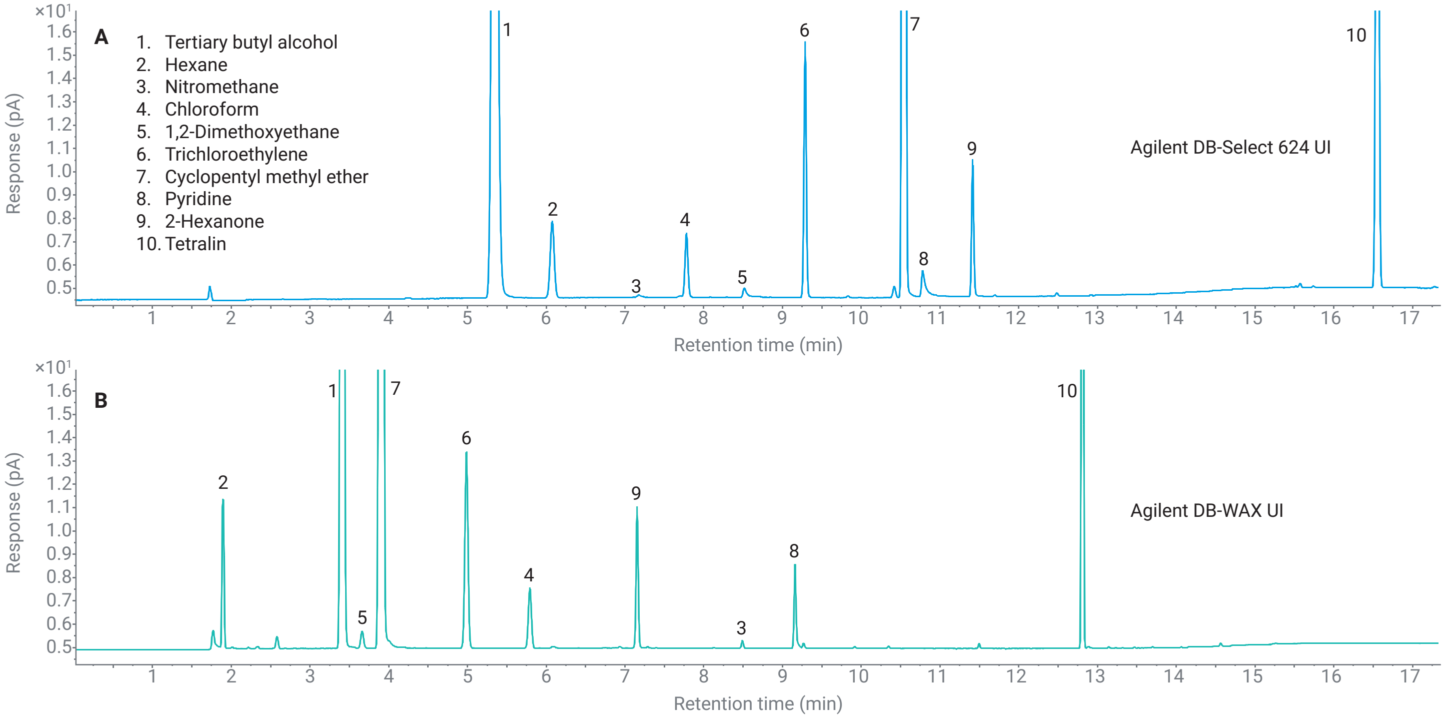


Figure 6. GC/FID chromatograms of class 2B standard solution on an Agilent DB-Select 624 UI column (procedure A) and an Agilent DB-WAX UI column (procedure B) using helium carrier gas.

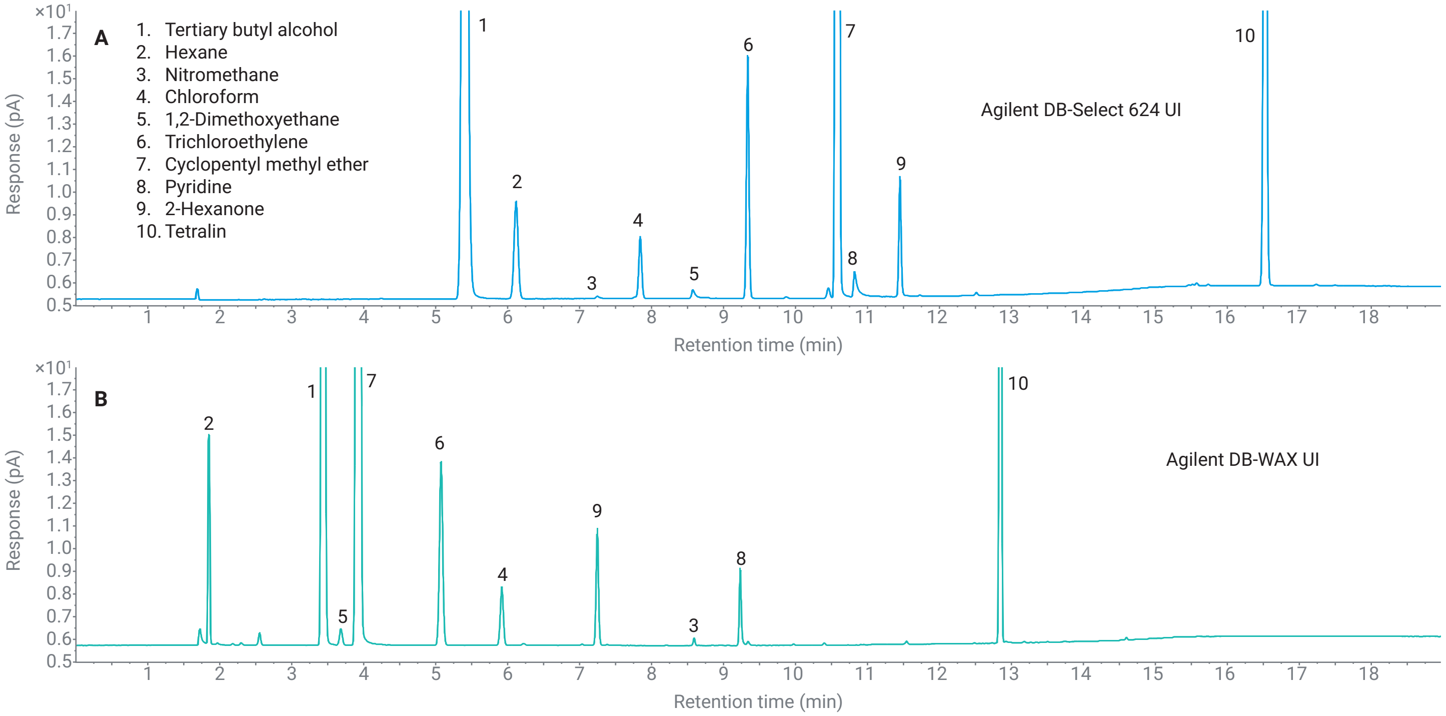


Figure 7. GC/FID chromatograms of class 2B standard solution on an Agilent DB-Select 624 UI column (procedure A) and an Agilent DB-WAX UI column (procedure B) using nitrogen carrier gas.

Table 3. RT and area repeatability (n = 9) obtained on Agilent DB-Select 624 UI and Agilent DB-WAX UI columns using helium and nitrogen carrier gas.

	He Carrier Gas				**N_2 Carrier Gas**			
	Procedure A DB-Select 624 UI		**Procedure B DB-WAX UI**		**Procedure A DB-Select 624 UI**		**Procedure B DB-WAX UI**	
Compound Name	**RT %RSD**	**Area %RSD**	**RT %RSD**	**Area %RSD**	**RT %RSD**	**Area %RSD**	**RT %RSD**	**Area %RSD**
Class 1								
1,1-Dichloroethene	0.021	1.275	0.016	1.931	0.034	2.186	0.034	1.714
1,1,1-Trichloroethane	0.005	1.373	0.008	1.409	0.005	2.201	0.012	1.799
Carbon tetrachloride	0.016	1.955	Coelutes with 1,1,1-trichloroethane	Coelutes with 1,1,1-trichloroethane	0.03	2.825	Coelutes with 1,1,1-trichloroethane	Coelutes with 1,1,1-trichloroethane
Benzene	0.004	1.833	0.013	1.36	0.006	1.828	0.01	2.002
1,2-Dichloroethane	0.003	2.107	0.01	1.768	0.007	2.807	0.009	2.265
Class 2A								
Methanol	0.047	2.521	0.04	2.558	0.014	2.629	0.021	2.647
Acetonitrile	0.014	1.406	0.017	1.38	0.003	1.765	0.004	1.797
Methylene chloride	0.007	0.777	0.012	0.765	0.003	0.324	0.004	0.37
trans-1,2-Dichloroethene	0.01	0.845	Coelutes with tetrahydrofuran	Coelutes with tetrahydrofuran	0.005	0.53	Coelutes with tetrahydrofuran	Coelutes with tetrahydrofuran
cis-1,2-Dichloroethene	0.004	0.696	0.014	0.719	0.004	0.399	0.003	0.389
Tetrahydrofuran	0.009	0.937	0.009	0.837	0.004	0.485	0.005	0.504
Cyclohexane	0.006	0.882	0.009	0.879	0.007	0.398	0.004	0.399
Methylcyclohexane	0.003	1.89	0.01	1.868	0.002	0.403	0.003	0.418
1,4-Dioxane	0.006	2.393	0.009	2.002	0.003	2.483	0.007	2.77
Methyl isobutyl ketone	0.002	0.704	0.011	0.712	0.003	0.338	0.005	0.332
Toluene	0.003	0.641	0.01	0.636	0.003	0.398	0.005	0.393
Chlorobenzene	0.001	0.655	0.073	0.644	0.002	0.406	0.02	0.411
Ethylbenzene	0.002	0.643	0.007	0.635	0.002	0.408	0.003	0.404
m-Xylene	0.002	0.645	0.005	0.632	0.003	0.416	0.002	0.409
p-Xylene	Coelutes with *m*-xylene	Coelutes with *m*-xylene	0.005	0.692	Coelutes with *m*-xylene	Coelutes with *m*-xylene	0.003	0.436
o-Xylene	0.002	0.541	0.088	0.522	0.002	0.386	0.024	0.38
Cumene	0.002	0.788	0.1	0.787	0.003	0.402	0.028	0.42
Class 2B								
Tertiary butyl alcohol	0.038	1.025	0.008	1.033	0.078	1.064	0.012	1.051
Hexane	0.007	2.59	0.016	2.575	0.011	1.779	0.015	1.57
Nitromethane	0.026	3.016	0.012	2.598	0.02	2.942	0.017	2.38
Chloroform	0.004	1.728	0.008	1.722	0.007	1.833	0.014	1.604
1,2-Dimethoxyethane	0.008	1.912	0.014	2.256	0.017	2.802	0.018	1.729
Trichloroethylene	0.003	2.141	0.008	2.092	0.003	2.076	0.016	2.084
Cyclopentyl methyl ether	0.003	0.58	0.006	0.581	0.004	0.75	0.012	0.746
Pyridine	0.004	1.167	0.048	1.786	0.007	3.291	0.104	2.264
2-Hexanone	0.002	0.61	0.005	0.643	0.002	0.879	0.009	0.682
Tetralin	0.003	1.025	0.012	1.03	0.003	1.227	0.024	1.194

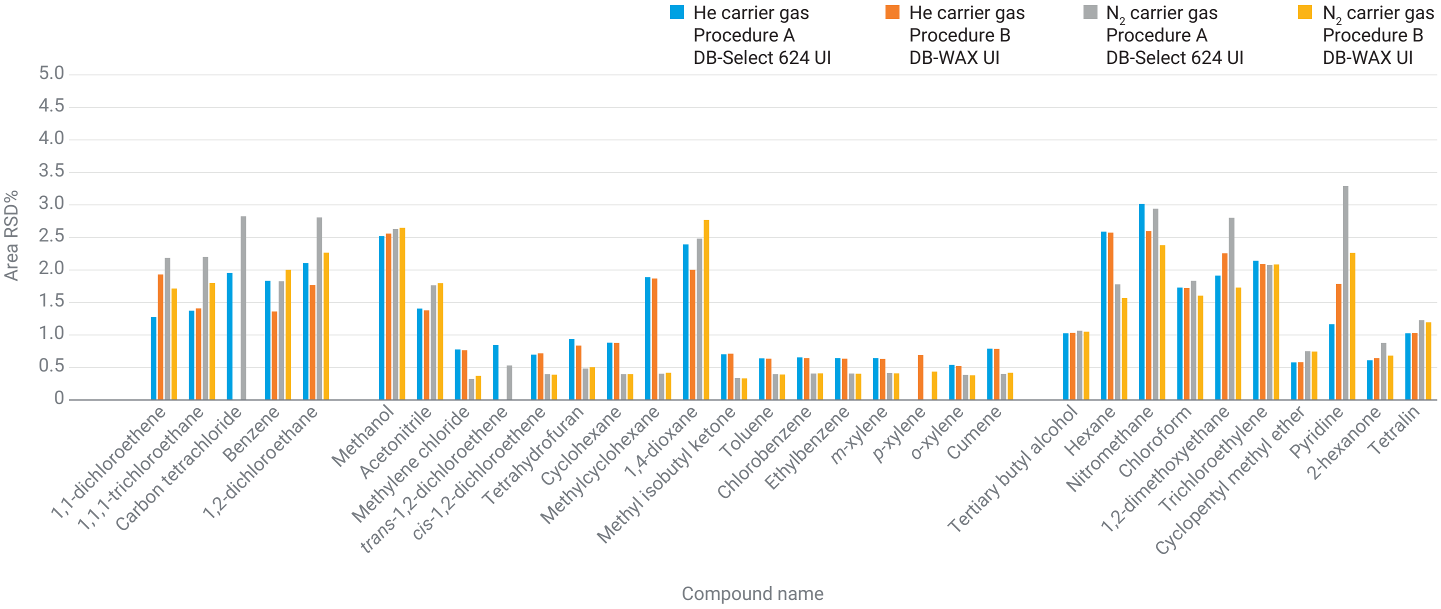


Figure 8. Area RSDs for all solvents on both Agilent DB-Select 624 UI and Agilent DB-WAX UI columns using helium and nitrogen carrier gas.

Single run analysis of mixed residual solvents

In routine pharmaceutical laboratories, class 1, 2A, and 2B residual solvents are not typically analyzed in separate injections. In most real-world applications, the residual solvents of interest usually include compounds from both class 1 and 2 categories. Therefore, standards containing class 1, 2A, and 2B solvents were combined into a single mixed standard consisting of 32 compounds. As shown in Figure 9 and Figure 10, the majority of the compounds were baseline separated. However, a few compound pairs coeluted. Importantly, the system used in this study is a dual-column configuration. Some compounds that coeluted on the DB-Select 624 UI column were well separated on the DB-WAX UI column, while components that were not resolved on the DB-WAX UI column could be effectively separated on the DB-Select 624 UI column. These complementary separation characteristics clearly demonstrate the advantages of dual-column analysis, providing improved resolution and higher confidence in compound identification for complex residual solvent mixtures. It should be noted that under the current conditions, several compounds, such as cis-1,2-dichloroethene, tetrahydrofuran, and CPME, coelute with other components on both columns. In such cases, MSD can be used to provide additional qualitative confirmation.

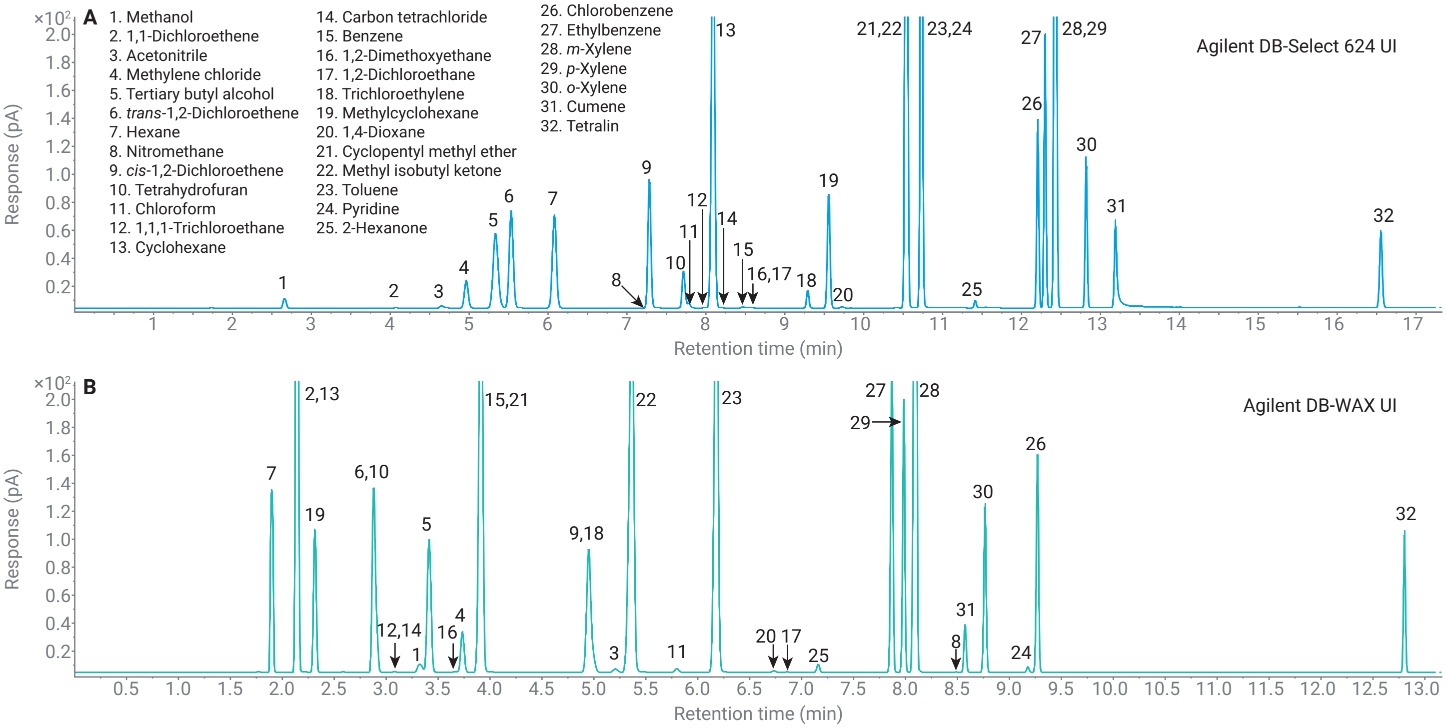


Figure 9. GC/FID chromatograms of class 1, 2A, and 2B mixture on an Agilent DB-Select 624 UI column (procedure A) and an Agilent DB-WAX UI column (procedure B) using helium carrier gas.

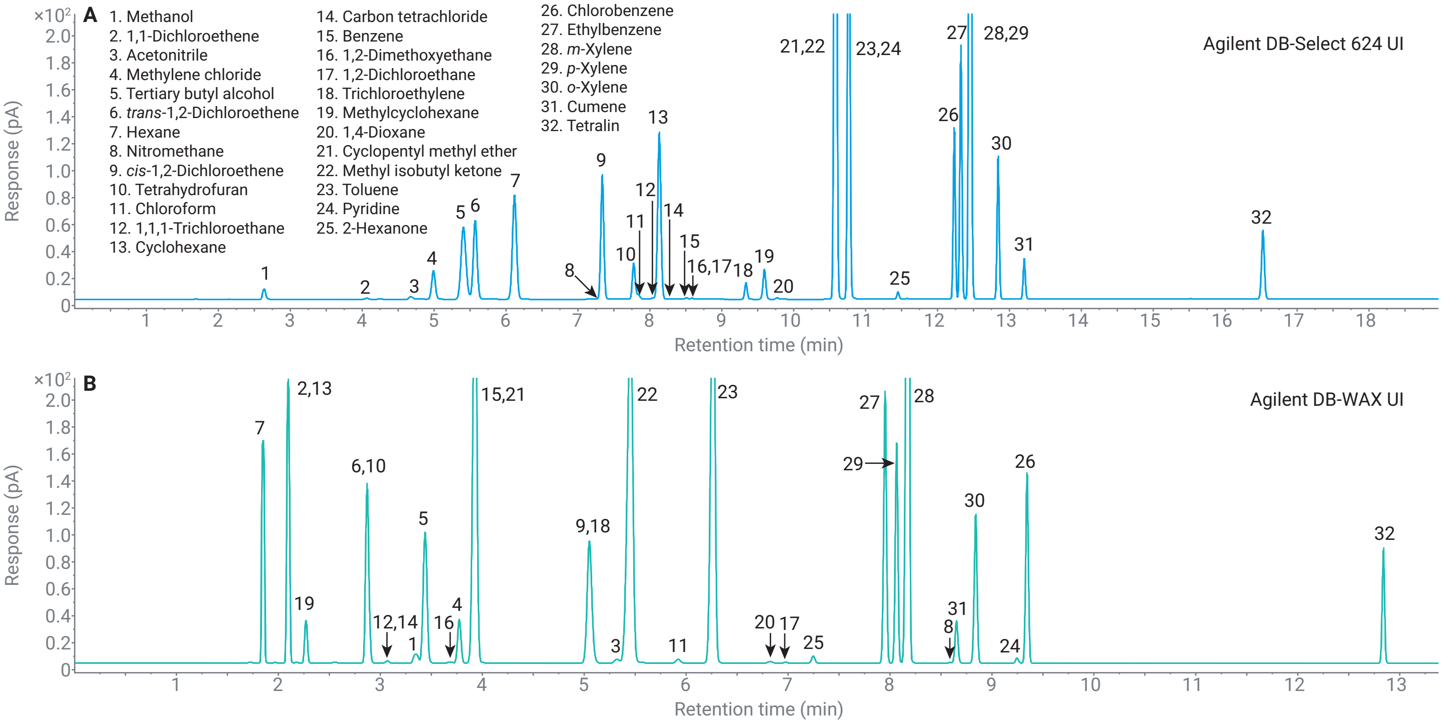


Figure 10. GC/FID chromatograms of class 1, 2A, and 2B mixture on an Agilent DB-Select 624 UI column (procedure A) and an Agilent DB-WAX UI column (procedure B) using nitrogen carrier gas.

GC Assist for performance monitoring and guided troubleshooting

In routine pharmaceutical laboratory workflows, daily GC operation typically begins with system suitability testing, performed either prior to daily analysis or at the start of each analytical sequence to confirm acceptable instrument performance. These checks commonly include resolution of critical compound pairs, retention time stability, peak area consistency, and others. Failure to meet predefined system suitability criteria generally requires investigation and documentation in accordance with GMP procedures.

Although the method described in this study follows the USP <467> and ChP 0861 requirements and applies a dual-column configuration for compound identification, many pharmaceutical laboratories are highly familiar with their products and have a well-defined understanding of the residual solvents present in their samples. Consequently, GC configurations using a single column are widely adopted for routine residual solvent analysis.

Although the 8890B GC is currently not capable of performing a complete evaluation of all system suitability criteria, it can support a set of key performance checks for a single-channel configuration. These include assessing whether the target peak retention time, peak area, symmetry, and the resolution of critical compound pairs fall within predefined acceptance ranges. If any parameter is found to be outside the allowable limits, the sequence can be configured to either continue or be aborted. Upon completion of the evaluation, a report is generated indicating a pass or fail result. In the case of a fail outcome, users can manually initiate the built-in self-guided troubleshooting function. The instrument identifies issues according to peak evaluation results and continuously interacts with the user, guiding them step by step through the troubleshooting process to collaboratively complete fault diagnosis.

The whole process begins with the acquisition of a reference chromatogram. In OpenLab CDS version 2.8, this is performed by selecting **GC Plugins** and launching **Peak Evaluation Setup**, which provides a fully user-guided workflow, as shown in Figure 11. The software presents a sequence of dialog windows, allowing users to proceed step by step without requiring prior expertise.

As illustrated in Figure 11, the **Peak Evaluation Setup** consists of three main steps.

- In the first step, a reference chromatogram is acquired by specifying the vial position of the standard solution and the associated acquisition method. Once initiated by the user, the GC performs the analysis, and the resulting reference chromatogram is stored directly within the GC system.
- In the second step, the user performs a series of actions, including integrating the reference chromatogram, identifying and naming the target compounds, saving the finalized reference chromatogram. The reference chromatogram is then applied to the acquisition method to ensure consistent performance evaluation during routine operation.
- In the third step, the user configures the acquisition method by enabling the Peak Evaluation function and defining the performance acceptance limit (for example, the allowable retention time deviation is ±2%, as shown in *"6. Set acceptance limits"* in Figure 11). Once these settings are defined, the method is saved and can be used for key performance evaluation during routine operation.

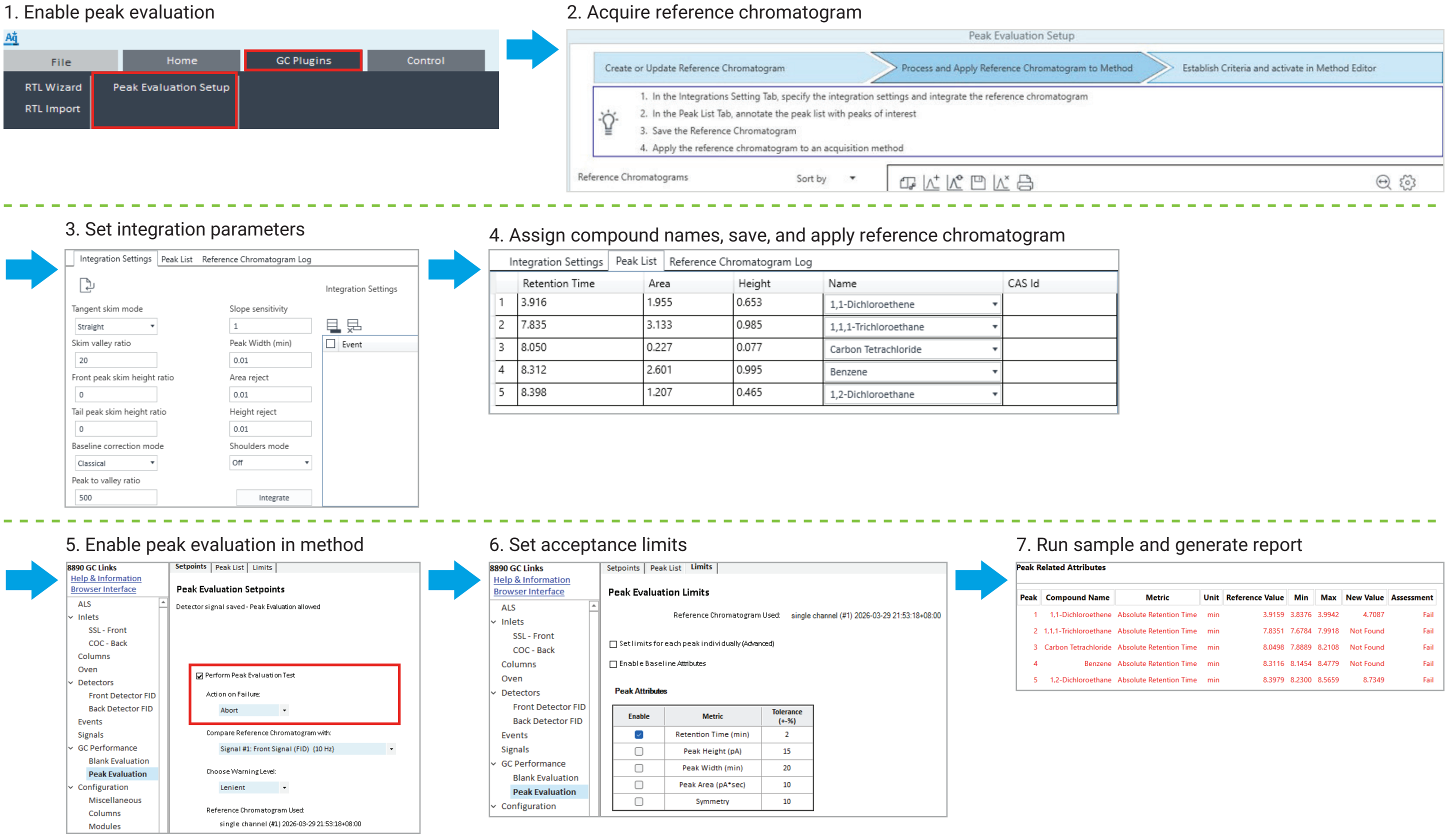
Once configured, the acquisition method can be used for key performance evaluations. If all monitored performance parameters remain within the predefined acceptance limits, a **Pass** report is automatically generated. If one or more criteria fall outside the specified limits, the system generates a **Fail** result. In such cases, a notification window automatically appears on the GC touchscreen, indicating that peak evaluation has failed, as shown in Figure 12.

The following troubleshooting workflow is intended as a representative case study. Depending on the specific issue encountered, the touchscreen may display different dialogs, messages, and recommended actions. By manually clicking **View Conditions** in the lower left corner of the alert window, more detailed information can be accessed. As shown in the screenshot "2. *Start troubleshooting*" in Figure 12, the fail result was due to the retention time being outside the allowable range. When the user selects **Troubleshoot**, the next dialog indicates that the GC has identified the current issue as **No Peaks**. The user can then click **Next**, after which the GC asks whether to proceed with troubleshooting to identify the cause of the missing peaks within the current flow path. The touchscreen then sequentially presents method parameters for the user to verify whether they are correct. If the user confirms that the parameters are correct, they can simply click **Next** to proceed. Once the method has been verified, the GC asks whether a system leak is suspected, guiding the user step by step through the troubleshooting process.

If a column-related issue is suspected and column trimming or reinstallation is required by the user, the Agilent 8890B GC initiates a controlled oven cool-down sequence to ensure safe handling. During the subsequent guided procedure, the system clearly informs the user of the specific tools required for column installation and provides step-by-step instructions directly on the touchscreen. An instructional column installation video is displayed on the touchscreen and can be viewed either in full-screen mode or paused as needed, allowing users to conveniently follow the installation steps while performing the task at the instrument.

In addition, the 8890B GC features an integrated oven light within the GC oven, with adjustable brightness to suit user preference. This enhanced illumination significantly improves visibility during column installation, enabling users to clearly see connection points and column positioning. Following column installation, an automatic inlet leak test is performed by the GC system to confirm the absence of leaks.

Throughout this process, the system provides step-by-step guidance, allowing users to systematically isolate and resolve the issue. This integrated workflow demonstrates how the Agilent 8890B intelligent GC simplifies daily work and troubleshooting, enabling efficient, compliant operation even within routine pharmaceutical laboratory environments.



1. Enable peak evaluation

2. Acquire reference chromatogram

Peak Evaluation Setup

Create or Update Reference Chromatogram > Process and Apply Reference Chromatogram to Method > Establish Criteria and activate in Method Editor

1. In the Integrations Setting Tab, specify the integration settings and integrate the reference chromatogram
2. In the Peak List Tab, annotate the peak list with peaks of interest
3. Save the Reference Chromatogram
4. Apply the reference chromatogram to an acquisition method

3. Set integration parameters

Integration Settings | Peak List | Reference Chromatogram Log

Integration Settings

Tangent skim mode: Straight
Skim valley ratio: 20
Front peak skim height ratio: 0
Tail peak skim height ratio: 0
Baseline correction mode: Classical
Peak to valley ratio: 500
Slope sensitivity: 1
Peak Width (min): 0.01
Area reject: 0.01
Height reject: 0.01
Shoulders mode: Off
Integrate
☐ Event

4. Assign compound names, save, and apply reference chromatogram

Integration Settings | Peak List | Reference Chromatogram Log

	Retention Time	Area	Height	Name	CAS Id
1	3.916	1.955	0.653	1,1-Dichloroethene	
2	7.835	3.133	0.985	1,1,1-Trichloroethane	
3	8.050	0.227	0.077	Carbon Tetrachloride	
4	8.312	2.601	0.995	Benzene	
5	8.398	1.207	0.465	1,2-Dichloroethane	

5. Enable peak evaluation in method

Peak Evaluation Setpoints

Detector signal saved - Peak Evaluation allowed

☑ Perform Peak Evaluation Test

Action on Failure: Abort

Compare Reference Chromatogram with: Signal #1: Front Signal (FID) {10 Hz}

Choose Warning Level: Lenient

Reference Chromatogram Used: single channel (#1) 2026-03-29 21:53:18+08:00

6. Set acceptance limits

Peak Evaluation Limits

Reference Chromatogram Used: single channel (#1) 2026-03-29 21:53:18+08:00

☐ Set limits for each peak individually (Advanced)

☐ Enable Baseline Attributes

Peak Attributes

Enable	Metric	Tolerance (+-%)
☑	Retention Time (min)	2
☐	Peak Height (pA)	15
☐	Peak Width (min)	20
☐	Peak Area (pA*sec)	10
☐	Symmetry	10

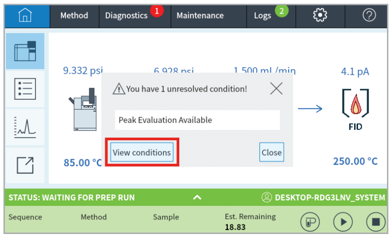
7. Run sample and generate report

Peak Related Attributes

Peak	Compound Name	Metric	Unit	Reference Value	Min	Max	New Value	Assessment
1	1,1-Dichloroethene	Absolute Retention Time	min	3.9159	3.8376	3.9942	4.7087	Fail
2	1,1,1-Trichloroethane	Absolute Retention Time	min	7.8351	7.6784	7.9918	Not Found	Fail
3	Carbon Tetrachloride	Absolute Retention Time	min	8.0498	7.8889	8.2108	Not Found	Fail
4	Benzene	Absolute Retention Time	min	8.3116	8.1454	8.4779	Not Found	Fail
5	1,2-Dichloroethane	Absolute Retention Time	min	8.3979	8.2300	8.5659	8.7349	Fail

Figure 11. Representative steps in the peak evaluation workflow.

1. Evaluate peak failure



You have 1 unresolved condition!

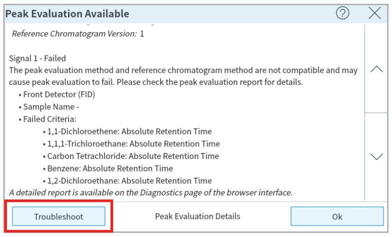
Peak Evaluation Available

STATUS: WAITING FOR PREP RUN

DESKTOP-RDG3LNV_SYSTEM

Est. Remaining 18.83

2. Start troubleshooting



Peak Evaluation Available

Reference Chromatogram Version: 1

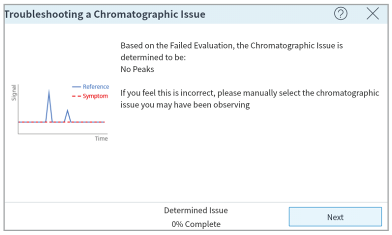
Signal 1 - Failed

The peak evaluation method and reference chromatogram method are not compatible and may cause peak evaluation to fail. Please check the peak evaluation report for details.

- Front Detector (FID)
- Sample Name -
- Failed Criteria:
  - 1,1-Dichloroethene: Absolute Retention Time
  - 1,1,1-Trichloroethane: Absolute Retention Time
  - Carbon Tetrachloride: Absolute Retention Time
  - Benzene: Absolute Retention Time
  - 1,2-Dichloroethane: Absolute Retention Time

A detailed report is available on the Diagnostics page of the browser interface.

3. Identify failure cause



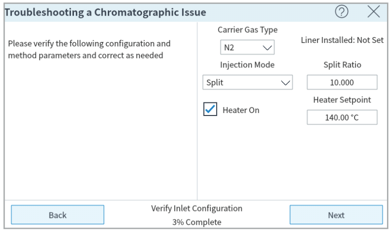
Troubleshooting a Chromatographic Issue

Based on the Failed Evaluation, the Chromatographic Issue is determined to be:
No Peaks

If you feel this is incorrect, please manually select the chromatographic issue you may have been observing

Determined Issue
0% Complete

4. Check method parameters



Troubleshooting a Chromatographic Issue

Please verify the following configuration and method parameters and correct as needed

Carrier Gas Type: N2

Liner Installed: Not Set

Injection Mode: Split

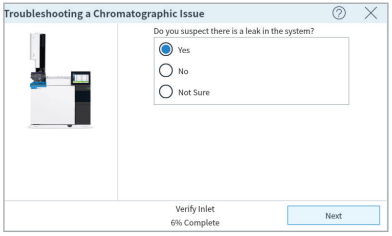
Split Ratio: 10.000

☑ Heater On

Heater Setpoint: 140.00 °C

Verify Inlet Configuration
3% Complete

5. Suspect system leak



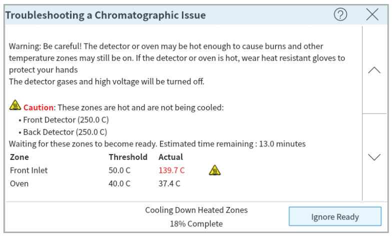
Troubleshooting a Chromatographic Issue

Do you suspect there is a leak in the system?

● Yes
○ No
○ Not Sure

Verify Inlet
6% Complete

6. Auto cool down



Troubleshooting a Chromatographic Issue

Warning: Be careful! The detector or oven may be hot enough to cause burns and other temperature zones may still be on. If the detector or oven is hot, wear heat resistant gloves to protect your hands
The detector gases and high voltage will be turned off.

⚠ Caution: These zones are hot and are not being cooled:

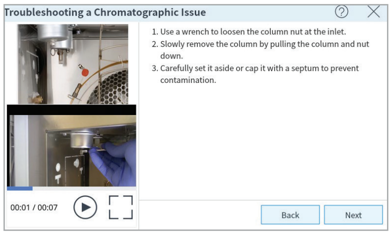
- Front Detector (250.0 C)
- Back Detector (250.0 C)

Waiting for these zones to become ready. Estimated time remaining : 13.0 minutes

Zone	Threshold	Actual	
Front Inlet	50.0 C	139.7 C	⚠
Oven	40.0 C	37.4 C	

Cooling Down Heated Zones
18% Complete

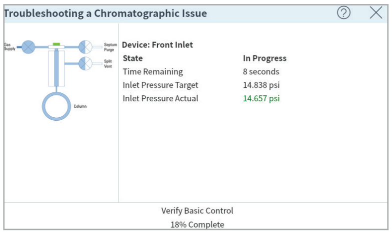
7. Column installation video



Troubleshooting a Chromatographic Issue

1. Use a wrench to loosen the column nut at the inlet.
2. Slowly remove the column by pulling the column and nut down.
3. Carefully set it aside or cap it with a septum to prevent contamination.

8. Automatic inlet leak test



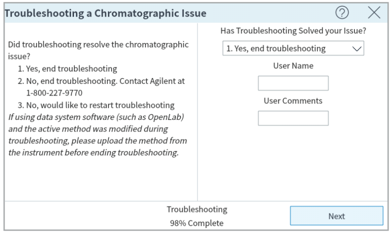
Troubleshooting a Chromatographic Issue

Device: Front Inlet

State	In Progress
Time Remaining	8 seconds
Inlet Pressure Target	14.838 psi
Inlet Pressure Actual	14.657 psi

Verify Basic Control
18% Complete

9. End troubleshooting



Troubleshooting a Chromatographic Issue

Did troubleshooting resolve the chromatographic issue?

1. Yes, end troubleshooting
2. No, end troubleshooting. Contact Agilent at 1-800-227-9770
3. No, would like to restart troubleshooting

If using data system software (such as OpenLab) and the active method was modified during troubleshooting, please upload the method from the instrument before ending troubleshooting.

Has Troubleshooting Solved your Issue?: 1. Yes, end troubleshooting

User Name

User Comments

Troubleshooting
98% Complete

Figure 12. Representative steps in the guided troubleshooting workflow.

Conclusion

This application note demonstrates a harmonized headspace GC/FID workflow suitable for residual solvent analysis in compliance with both the 2025 revision of United States Pharmacopoeia (USP) <467> and the Chinese Pharmacopoeia (ChP 2025, General Chapter 0861). By implementing a dual-column, dual-FID configuration on a single inlet, screening and confirmatory analyses can be performed simultaneously, significantly reducing total analysis time compared to traditional sequential approaches while maintaining orthogonal separation selectivity.

The integrated Agilent 8697 headspace sampler and 8890B GC platform provides consistent chromatographic performance with both helium and nitrogen carrier gases, supporting flexible laboratory operation without compromising data quality. Beyond analytical performance, the intelligent capabilities of the 8890B GC enhance operational reliability and simplify daily use. Through continuous interaction with the user, the built-in GC Assist function operates in a guided, wizard-like manner, leading users step by step through the troubleshooting process for effective fault diagnosis. Together, these features enable a compliant, time-efficient, and user-friendly solution for residual solvent testing under the latest USP <467> and ChP 0861 requirements.

References

1. USP-NF<467>Residual Solvents. United States Pharmacopeia and National Formulary, **2025**.
2. General Chapter 0861: Residual Solvents. Chinese Pharmacopoeia, **2025**.
3. International Council for Harmonisation (ICH) Q3C: Impurities—Residual Solvents

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