Satisfy requirements for residual solvent analysis

Agilent J&W DB-Select 624 Ultra Inert for <467>
and DB-WAX Ultra Inert Capillary GC Columns
Be confident that residual solvents will not affect the safety, stability, or effectiveness of your products

The manufacturing process of active pharmaceutical ingredients (APIs) may contribute to residual solvents remaining in the final pharmaceutical product. Producers need to monitor and control the levels of residual solvents for a number of reasons including safety, effect on crystalline form, solubility, bioavailability, and stability. Residual solvents can be classified* as follows:

- **Class 1** solvents are considered hazardous, and should be avoided during manufacturing
- **Class 2** solvents are considered less severely toxic, and should be limited
- **Class 3** solvents pose less risk to human health than class 1 or class 2 solvents

United States Pharmacopeia (USP) Method <467> is the method used worldwide for quality control, and closely follows ICH Q3C guidelines. The method is composed of three analytical procedures for identification and quantification.

- **Procedure A**: Identification and limit testing; uses a G43 phase (624-type column)
- **Procedure B**: Confirms whether an identified solvent is above the regulated limits; uses a G16 phase (WAX-type column)
- **Procedure C**: Quantitative test using a G43 phase or G16 phase, depending on which produced fewer coelutions

USP <467> analytical flowchart for residual solvent analysis.

*Q3C—Tables and List Guidance for Industry, Rev 3, US Department of Health and Human Services, CDER & CBER, FDA, June 2017
Increase performance and productivity for your analysis of residual solvents with Agilent J&W DB-Select 624 Ultra Inert for <467> and DB-WAX Ultra Inert columns

Agilent J&W Ultra Inert columns are engineered for better peak shapes, and are rigorously tested with demanding probes to verify best-in-class inertness. On the following pages, you’ll see how these innovative columns delivered outstanding resolution, sensitivity, and repeatability for residual solvent analysis.
USP <467> Procedure A
High repeatability for identification and limit testing

Procedure A is the first step in the identification process. It is performed on a G43 phase (624-type column) to determine whether residual solvents are present at detectable levels.

**Single-column GC/FID analysis of residual solvents**

In this example, Agilent J&W DB-Select 624 UI columns delivered excellent resolution of the residual solvent peaks. The Agilent 7697A headspace sampler was also a key factor in achieving the lower limits of concentration for these tests. Its inert sample path, thermal zone stability, and flexible EPC-controlled vial sampling all contribute to reliable system performance.

**Conditions:**
- **Column:** Agilent J&W DB-Select 624 UI for <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
- **FID:** 250 °C, H₂ 30 mL/min, air 400 mL/min, N₂ 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)
These chromatograms represent all three solvent classes tested using Procedure A. Excellent peak shape was achieved by combining Agilent J&W DB-Select 624 UI columns with the Agilent 7697A headspace sampler.

Class 1

Class 2A

Class 2B

Class 1 (top), class 2A (middle), and class 2B (bottom) solvents at USP <467> limit concentrations.
Once a residual solvent is identified and determined to be above the percent daily exposure limit, Procedure B is performed to confirm analyte identity.

**Single-column GC/FID analysis of residual solvents**

Here, USP <467> procedure B was used to confirm the peak identification of procedure A. An Agilent J&W DB-WAX UI GC column was used as a confirmation column.

### Conditions

<table>
<thead>
<tr>
<th>GC system:</th>
<th>Agilent 7890B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Column:</td>
<td>Agilent J&amp;W DB-WAX UI, 30 m x 0.32 mm, 0.25 µm (p/n 123-7032UI)</td>
</tr>
<tr>
<td>Liner:</td>
<td>Agilent liner, splitless, straight, deactivated, quartz (p/n 5181-8818)</td>
</tr>
<tr>
<td>Equivalent:</td>
<td>Agilent Ultra Inert liner, splitless, straight, 1 mm id (p/n 5190-4047)</td>
</tr>
<tr>
<td>Inlet:</td>
<td>Split/splitless, 140 °C, split ratio 5:1</td>
</tr>
<tr>
<td>Oven:</td>
<td>50 °C (hold 20 min) to 165 °C at 6 °C/min (hold 20 min)</td>
</tr>
<tr>
<td>FID:</td>
<td>250 °C</td>
</tr>
<tr>
<td>Headspace:</td>
<td>Agilent 7697A Headspace Sampler</td>
</tr>
<tr>
<td>Oven temperature:</td>
<td>80 °C</td>
</tr>
<tr>
<td>Loop temperature:</td>
<td>80 °C</td>
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<tr>
<td>Transfer line temperature:</td>
<td>100 °C</td>
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<tr>
<td>Equilibration time:</td>
<td>45 min</td>
</tr>
<tr>
<td>Sample loop:</td>
<td>1 mL</td>
</tr>
</tbody>
</table>

The Agilent J&W DB-WAX UI GC column demonstrated good resolution, peak shape, sensitivity, and repeatability for the three classes of residual solvents at method-specified limits.

### Class 1

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

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Class 1 standard solution resolved on an Agilent J&W DB-WAX Ultra Inert GC column. Carbon tetrachloride coelutes with 1,1,1-trichloroethane with the G16 column, but is separated from all peaks in the class 1 standard with the G43 column.

*Carbon tetrachloride coelutes with 1,1,1-trichloroethane with the G16 (DB-WAX UI) column, but is separated from all peaks in the class 1 standard with the G43 column.
Class 2A standard solution resolved on an Agilent J&W DB-WAX Ultra Inert 30 m × 0.32 mm, 0.25 μm GC column.

1. Cyclohexane
2. Methylcyclohexane
3. trans-1,2-Dichloroethene
4. Tetrahydrofuran
5. Methanol
6. Dichloromethane
7. cis-1,2-Dichloroethene
8. Acetonitrile
9. Toluene
10. 1,4-Dioxane
11. Ethylbenzene
12. p-xylene
13. m-xylene
14. o-xylene
15. Chlorobenzene

Class 2B standard solution resolved on an Agilent J&W DB-WAX Ultra Inert 30 m × 0.32 mm, 0.25 μm GC column.

1. Hexane
2. 1,2-Dimethoxyethane
3. Trichloroethylene
4. Chloroform
5. 2-Hexanone
6. Nitromethane
7. Pyridine
8. Tetralin
Dual-column GC/FID analysis of residual solvents

With the dual-channel GC/FID configuration, static headspace analysis performed at 85 °C for 40 minutes improved repeatability and reduced analysis time and cycle time. A DB-WAX UI GC column was used as a confirmation column in this system. USP <467> procedures A and B can be accomplished in one run with the dual channel configuration.

**Conditions**

**GC system:** Agilent 7890B

**Column 1:** Agilent J&W DB-WAX UI, 30 m × 0.32 mm, 0.25 µm (p/n 123-7032UI)

**Column 2:** Agilent J&W DB-Select 624 UI, 30 m × 0.32 mm, 1.8 µm (p/n 123-0334UI)

**Liner:** Agilent liner, splitless, straight, deactivated, quartz (p/n 5181-8818)

Equivalent: Agilent Ultra Inert liner, splitless, straight, 1 mm id (p/n 5190-4047)

**Tubing:** Agilent Ultimate Plus deactivated fused silica tubing, 0.5 m × 0.32 mm (p/n CP803205)

**Carrier gas:** Helium, constant flow mode, 15 psi

**Inlet:** Split/splitless, 140 °C, split ratio 2.5:1

**Oven:** 40 °C (hold 5 min) to 240 °C at 18 °C/min (hold 2 min)

**FID (both channels):** 250 °C

**Headspace:** Agilent 7697A Headspace Sampler

**Oven temperature:** 85 °C

**Loop temperature:** 85 °C

**Transfer line temperature:** 100 °C

**Equilibration time:** 40 min

**Sample loop:** 1 mL

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**Class 1**

Class 1 standard solution analyzed using an Agilent J&W DB-WAX UI and an Agilent DB-Select 624 UI GC column.
The high inertness of the DB-WAX UI column provided excellent peak shape for residual solvents. For pyridine—a particularly challenging compound—USP tailing was 1.06.

Class 2A standard solution analyzed using an Agilent J&W DB-WAX UI and an Agilent DB-Select 624 UI GC column.

Class 2B standard solution analyzed using an Agilent J&W DB-WAX UI and an Agilent DB-Select 624 UI GC column.

1. Cyclohexane
2. Methylcyclohexane
3. cis-1,2-Dichloroethene
4. Tetrahydrofuran
5. Methanol
6. Dichloromethane
7. cis-1,2-Dichloroethene
8. Acetonitrile
9. Toluene
10. 1,4-Dioxane
11. Ethylbenzene
12. p-xylene
13. m-xylene
14. o-xylene
15. Chlorobenzene

1. Hexane
2. 1,2-Dimethoxyethane
3. Trichloroethylene
4. Chloroform
5. 2-Hexanone
6. Nitromethane
7. Pyridine
8. Tetralin

Dual-channel GC/FID chromatograms of class 2B standard solution using an Agilent J&W DB-WAX UI and an Agilent DB-Select 624 UI GC column.
Agilent J&W DB-Select 624 UI columns showed excellent performance for residual solvent analysis according to USP <467> procedure A. Repeatability was generally better than 2.5% RSD for Class 1, Class 2A, and Class 2B solvents.

Once a residual solvent was identified above the permitted daily exposure (PDE) limit, procedure B was performed to confirm analyte identity. The Agilent J&W DB-WAX UI GC column was successfully used as a confirmation column, because it yields an alternate selectivity compared to that of a G43 column.

**First-class precision, reliability, and ease of use: Agilent 7697A GC Headspace Sampler**

With best-in-class technology and powerful software, the Agilent 7697A Headspace Sampler is packed with the latest productivity-boosting features.

- **Unique sampling design** allows you to use hydrogen as a carrier gas, delivering optimal chromatography and helping to future-proof your lab
- **Comprehensive software** goes beyond sample handling to guide you through tasks, such as method development and resource conservation
- **Method optimization tools** facilitate headspace method development
- **Electronic pneumatic control**, vial leak checking, and barometric pressure compensation ensure consistent results
Residual Solvent Analyzers

Streamline your USP <467> residual solvent detection

Based on the Agilent Intuvo 9000 GC system, Agilent Residual Solvent Analyzers are factory pre-tested and preconfigured to deliver results, fast, while saving precious start-up time. What's more, their analytical precision exceeds USP method requirements for the three classes of residual solvents.

Facilitate your QA/QC with these unique advantages

- Pre-configured to meet system suitability requirements for USP <467>, including column, consumables, calibration/checkout samples, and analytical method
- Chemically tested to ensure optimal analysis of Class 1 and Class 2A/B solvents
- Precise temperature and sampling control routines: The Agilent 7697A Headspace Sampler maximizes throughput and minimizes operator error
- Headspace thermal zone stability of ±0.1 °C, inert flowpath, and Capillary Flow Technology provide excellent RSD for Class 1A and 2A/B solvents—while minimizing carryover
- Begin system calibration and validation immediately following installation
Easily quantitate OVI content with Dual-FID Residual Solvent Analyzers

Dual-FID analyzers are ideal for identifying organic contaminants in active ingredients, formulations, and additives. The dual-FID configuration uses dissimilar columns for added confirmation within a single injection. In addition, an inert sample flowpath and thermal zone stability—combined with the automation capabilities of the Agilent 7697A Headspace Sampler—provide unsurpassed accuracy and repeatability.
Achieve USP <467> compliance with the complete Agilent residual solvents workflow

Calibrate
Separate
Identify
Analyze

Agilent-engineered GC supplies deliver what your pharmaceutical applications demand

Achieve ultimate deactivation performance with Agilent Ultra Inert Inlet Liners
Agilent’s Ultra Inert Inlet Liners prevent adsorption and ensure accurate sample transfer onto the GC column through a robust deactivated surface. These liners are recommended for trace level analysis of active analytes. Liners with inert wool retain non-volatiles, prolonging column life and lowering frequency of MS source maintenance. Visit www.agilent.com/chem/ultra-inert-liners

Calibration confidence starts with Agilent Certified standards
Ensure reliable results at every stage of your residual solvents analysis. All standards are manufactured and verified in accordance with ISO 9001 by an ISO 17025 accredited laboratory. Visit www.agilent.com/chem/r-s-standards

Why gamble with your results? Choose Agilent vials and accessories
Vials, caps, and septa are a critical part of your analytical workflow—no less important than your column or instrument. That is why all Agilent vials and accessories undergo a comprehensive quality control process covering all aspects of the product life cycle. Visit www.agilent.com/chem/vials

Make productivity happen with the Agilent ADM Flow Meter
Maintaining a NIST-certified flow meter is now easier and more convenient than ever. To recalibrate, simply replace the flow meter cartridge in your own lab—reducing downtime, shipping costs, and paperwork. Visit www.agilent.com/chem/admflowmeter

Protect the purity of your gas with the Agilent Gas Clean Filter
Inserting a Gas Clean Filter System in the gas line immediately before the instrument inlet greatly reduces the level of contaminants and impurities, improving trace analysis. Visit www.agilent.com/chem/gasclean
### Ordering Information

#### Residual solvent standards

<table>
<thead>
<tr>
<th>Description</th>
<th>Analytes/Certified Values</th>
<th>Part number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Revised Method &lt;467&gt; Class 1</td>
<td>Benzene: 10.0 mg/mL, Carbon tetrachloride: 20.1 mg/mL, 1,2-dichloroethane: 25.1 mg/mL, 1,1-dichloroethene: 40.2 mg/mL, 1,1,1-trichloroethane: 50.2 mg/mL, Solvent: Dimethyl sulfoxide (DMSO)</td>
<td>5190-0490</td>
</tr>
<tr>
<td>Revised Method &lt;467&gt; Class 2B</td>
<td>Chloroform: 301.4 μg/mL, 1,2-dimethoxyethane: 501.5 μg/mL, N-hexane: 1457 μg/mL, 2-hexanone: 251.1 μg/mL, Nitromethane: 251.2 μg/mL, Pyridine: 1005 μg/mL, Tetralin: 502.4 μg/mL, Trichloroethene: 401.9 μg/mL, Solvent: Dimethyl sulfoxide (DMSO)</td>
<td>5190-0491</td>
</tr>
<tr>
<td>Revised Method &lt;467&gt; Class 2A</td>
<td>Acetonitrile: 2.06 mg/mL, Chlorobenzene: 1.81 mg/mL, Cyclohexane: 19.5 mg/mL, Cis-1,2-dichloroethene: 4.72 mg/mL, Trans-1,2-dichloroethene: 4.72 mg/mL, 1,4-dioxane: 1.91 mg/mL, Ethyl benzene: 1.85 mg/mL, Methylene chloride: 3.01 mg/mL, Tetrahydrofuran: 3.62 mg/mL, Toluene: 4.47 mg/mL, O-xylene: 0.984 mg/mL, M-xylene: 6.53 mg/mL, P-xylene: 1.53 mg/mL, Solvent: Dimethyl sulfoxide (DMSO)</td>
<td>5190-0492</td>
</tr>
<tr>
<td>Revised Method &lt;467&gt; Class C</td>
<td>N,N-dimethylacetamide: 5461 μg/mL, N,N-dimethylformamide: 4417 μg/mL, 2-ethoxyethanol: 801.9 μg/mL, Ethylene glycol: 3112 μg/mL, Formamide: 1101 μg/mL, 2-methoxyethanol: 250.3 μg/mL, N-methylpyrrolidone: 2657 μg/mL, Sulfolane: 799.9 μg/mL, Solvent: Dimethyl sulfoxide (DMSO)</td>
<td>5190-0493</td>
</tr>
<tr>
<td>Revised Method &lt;467&gt; Class 2B LOW</td>
<td>Chloroform: 60.0 μg/mL, 1,2-dimethoxyethane: 100.0 μg/mL, Nitroethane: 291.0 μg/mL, 2-hexanone: 50.0 μg/mL, Pyrrole: 200.5 μg/mL, Tetralin: 100.5 μg/mL, Trichloroethylene: 80.0 μg/mL, Solvent: Dimethyl sulfoxide (DMSO)</td>
<td>5190-0513</td>
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#### Agilent J&W columns for Residual Solvent Revised Method <467>

<table>
<thead>
<tr>
<th>Description</th>
<th>Part number</th>
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<tbody>
<tr>
<td>DB-WAX UI, 30 m x 0.32 mm, 0.25 μm</td>
<td>123-7032UI</td>
</tr>
<tr>
<td>DB-select 624 UI, 30 m x 0.32 mm, 1.8 μm</td>
<td>123-0334UI</td>
</tr>
<tr>
<td>DB-624UI Ultra Inert, 30 m x 0.32 mm, 1.8 μm</td>
<td>123-1334UI</td>
</tr>
</tbody>
</table>

#### Vials, caps, and septa for Residual Solvent Revised Method <467>

<table>
<thead>
<tr>
<th>Description</th>
<th>Part number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headspace vial, crimp, clear, write-on spot, flat bottom, 20 mL, 23 x 75 mm, 100/pk</td>
<td>5190-2288</td>
</tr>
<tr>
<td>Headspace caps/septa, crimp, 20 mm, silver aluminum cap, PTFE/silicone septa, 100/pk</td>
<td>5183-4477</td>
</tr>
<tr>
<td>Headspace caps/septa crimp, 20 mm, steel magnetic cap, high-temperature septa, 100/pk</td>
<td>5190-3987</td>
</tr>
<tr>
<td>Headspace crimp top vial kit, 20 mL, clear, flat bottom, silver aluminum cap, PTFE/silicone septa, 100/pk</td>
<td>8010-0413</td>
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</table>

#### Crimpers, decappers, and accessories

<table>
<thead>
<tr>
<th>Description</th>
<th>Part number</th>
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<tbody>
<tr>
<td>Crimper, electronic with lithium battery, 11 mm</td>
<td>5190-3188</td>
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<tr>
<td>Crimper, electronic with lithium battery, 20 mm</td>
<td>5190-3189</td>
</tr>
<tr>
<td>Decapper, electronic with lithium battery, 11 mm</td>
<td>5190-3190</td>
</tr>
<tr>
<td>Decapper, electronic with lithium battery, 20 mm</td>
<td>5190-3191</td>
</tr>
<tr>
<td>Battery, electronic, replacement for crimper</td>
<td>5190-3192</td>
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<tr>
<td>Crimper, high power electronic, with power supply</td>
<td>5190-4061</td>
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<tr>
<td>Crimper jaw set, high power electronic, 11 mm</td>
<td>5190-4062</td>
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<tr>
<td>Decapper jaw set, high power electronic, 11 mm</td>
<td>5190-4063</td>
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<tr>
<td>Crimper jaw set, high power electronic, 20 mm</td>
<td>5190-4064</td>
</tr>
<tr>
<td>Decapper jaw set, high power electronic, 20 mm</td>
<td>5190-4065</td>
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