All About USP <467> & Residual Solvents

Regulatory and Application Updates

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Agilent
Trusted Answers

Pharmaceutical Impurities

What

- Unwanted chemicals (either introduced directly using contaminated raw materials or are formed during the mfg. process) that remain with APIs or Drug Product formulations
- Three major categories of pharmaceutical impurities, viz. -
  - Organic & Inorganic Compounds
  - Elemental Impurities
  - **Residual Solvents**

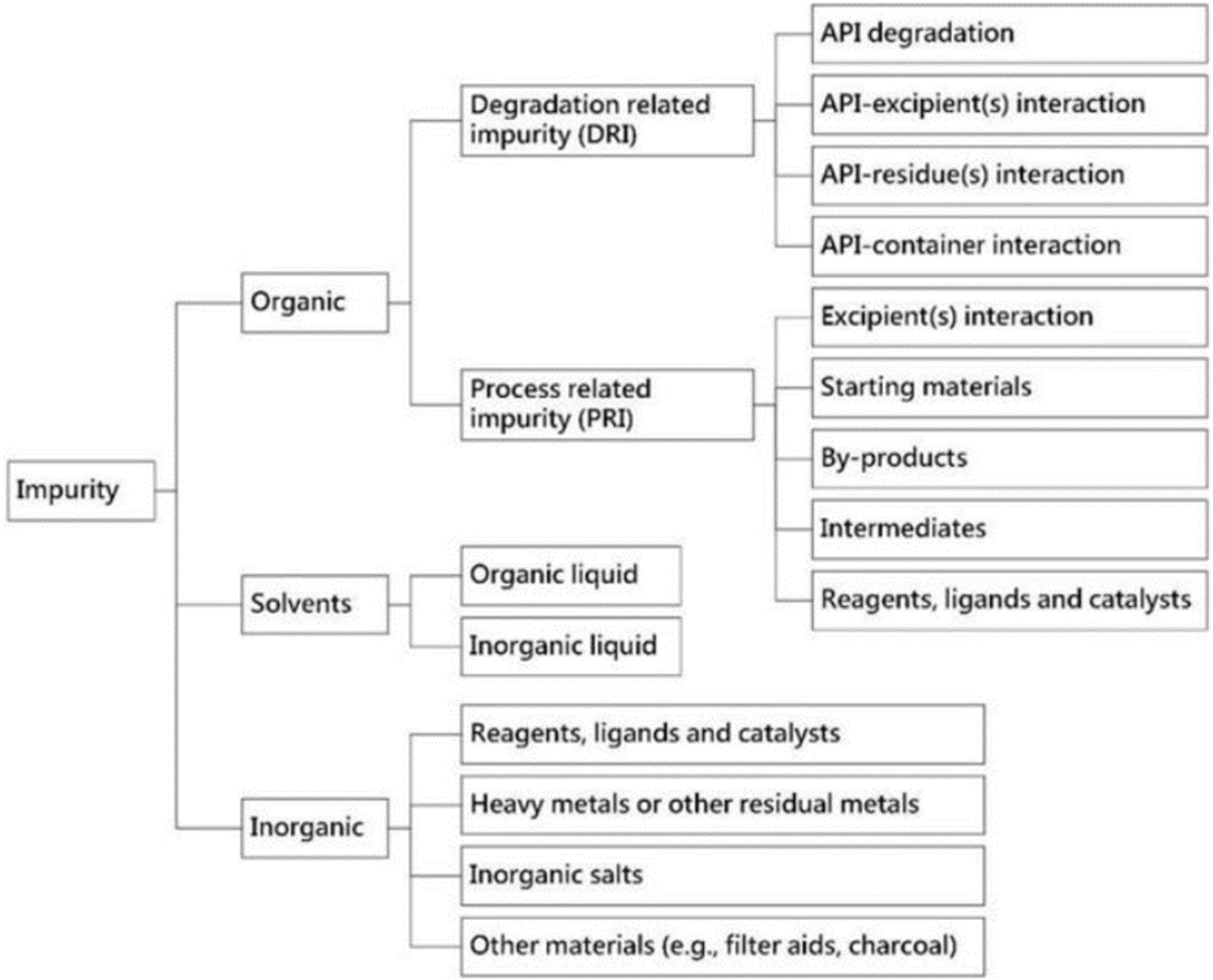
How

- May arise during synthesis or as a reaction by-product
- Formed as a result of the inherent instability of drug substances
- Added excipients, water
- Interactions with manufacturing equipment and packaging materials and container closure systems (CCSs)

Why

- The amount of impurity present in drug substance affects the quality and efficacy of the final pharmaceutical product and safety. Therefore, the identification, quantitation, qualification, and control of impurities are a critical part of the drug development process

Impurity Profiling (Pharmaceuticals)



Ref: (7) (PDF) Determination of Impurities in Pharmaceuticals: Why and How? (researchgate.net)

What are Residual Solvents?

Residual solvents – Organic volatile chemicals used or produced in manufacturing of API's, excipients or formulations.

Residual solvents can arise from various sources:

- Synthesis or Reaction byproduct
- Inherent instability exhibited by some drug substances
- Excipients and water used in the manufacturing process
- Interactions with manufacturing equipment and packaging materials, including container closure systems.

The primary guiding regulations for residual solvents include USP <467>, which aligns closely with ICH Q3C(R8) guidelines.
'*Since there is **no therapeutic benefit** from residual solvents, these should be removed to extent possible to meet Pdt Specs, GMP or other requirements*.'

The document classifies residual solvents into 3 categories:

- **Class 1:** Solvents to be avoided, *including known human carcinogens, strongly suspected human carcinogens, and solvents posing environmental hazards*.

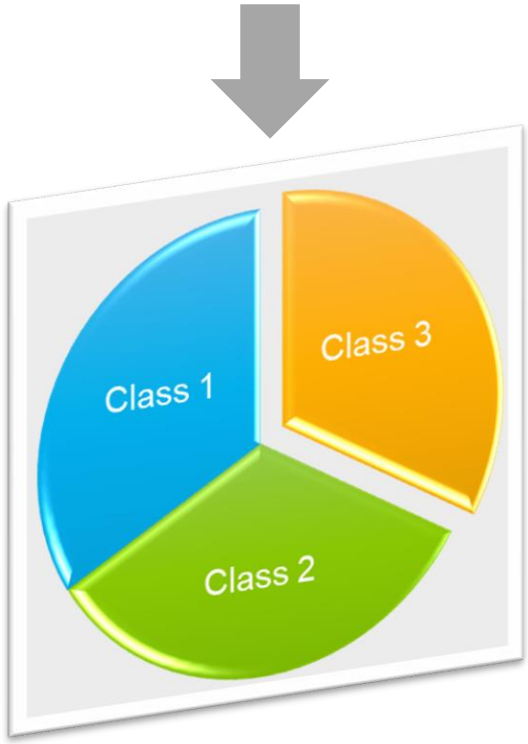
- **Class 2:** Solvents to be limited, *comprising nongenotoxic animal carcinogens or agents causing other irreversible toxicities such as neurotoxicity or teratogenicity. This class also includes solvents suspected of causing significant but reversible toxicities*.

- **Class 3:** Solvents with low toxic potential, *having no health-based exposure limit*.

Residual Solvent Analysis

USP <467> and ICH Q3C (R5 and R8) compliance for residual solvent analysis

Organic volatile chemicals used in the preparation of APIs, excipients & drug products



ICH

USP

Require Chromatographic Analysis

Class 1
- Solvents to be avoided
- Know or strongly perceived human carcinogens

Class2
- Solvents to be limited
- Non-genotoxic carcinogens or possible neurotoxic or teratogenic agents

Class 3
- Solvents with low toxic potential
- No health-based exposure limit is needed

Residual Solvents limits & Control Strategies

Permitted Limits – Method used to establish Permitted Daily Exposure (PDE) for residual solvents is derived from no-observed effect level (NOEL) or lowest-observed effect level (LOEL) in most relevant animal study (Toxicity Data).

'Class 1 solvents should be avoided, Meanwhile limits for Class 2 solvents are based on the toxicological permitted daily exposure (PDE), whereas Class 3 solvents are considered less toxic, and control to 50 mg/day or less for each of these solvents is acceptable without justification.'

Options to describe limits of solvents:
Option-1: Concentration (ppm) = 1000 X PDE/ Dose
Option-2: Adding the amount of residual solvents present in each component of drug product. The SUM of amounts of solvent per Day should be less than PDE.

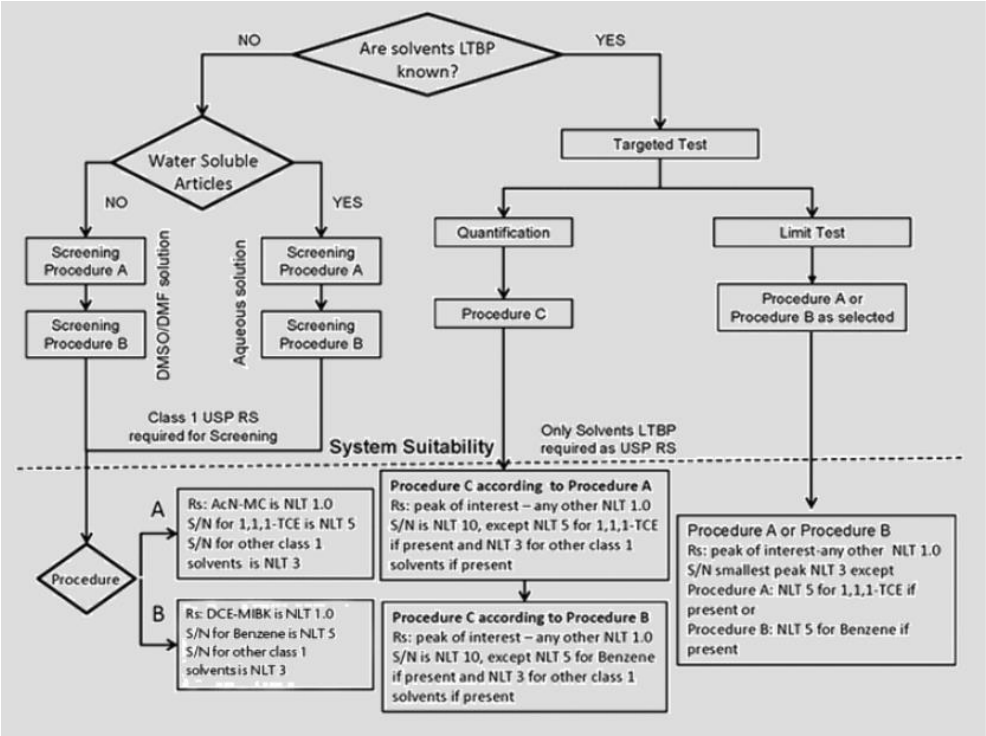
***Guidelines for Residual Solvents* (CPMP/ICH/283/95)**

- When a Class 1 solvent might be present in another solvent (*e.g.* Acetone or Toluene containing Benzene), routine testing is not required when – The limit applied to original solvent is such that class 1 solvent will be present in API at levels below guidelines limits.
- It is proved (with Validated method) that class 1 solvent is not more than 30% of spec limits, in intermediates or final pdt.
- Supporting data – 6 consecutive pilot scale or 3 consecutive Industry scale batches.
- When a Class 2 is LTBP, they should be routinely controlled in intermediate or final pdt. *e.g.*
  - LTBP in last step of synthesis it should be routinely controlled in Final API/ Pdt.
  - LTBP prior to last step, then need not to be reported in Drug Specs if levels are NMT 10% of acceptable limits (e.g. Acetonitrile 41 ppm)

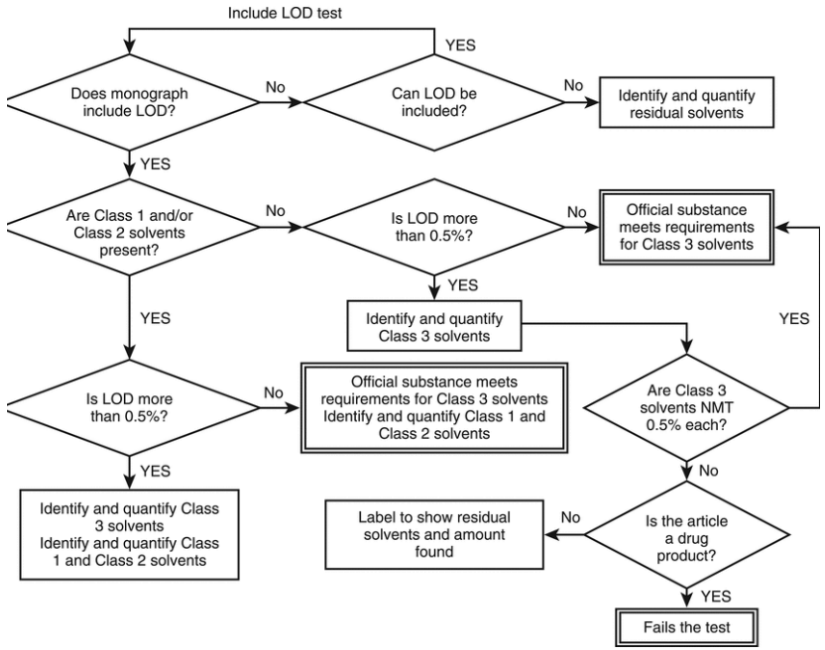
Residual Solvents limits & Control Strategies

<467> describes Analytical procedures (Procedures A, B, and C) for evaluating the levels of all Class 1 and the majority of Class 2 residual solvents. For each test matrix, verification is needed to demonstrate the reliability of the compendial procedure, as described in <1467>.

- When the solvents ***LTBP (likely to be present) are not known***, use the screening tests of Procedure A and B, as required.
- When the information about solvents ***LTBP in the material is known***, the system suitability requirements only need to be demonstrated for the solvents expected to be present.



USP<467> Figure 4. System suitability requirements based on the method of choice and previous knowledge about solvents LTBP.



USP<467> Figure 5. Decision tree for the control of Class 3 residual solvents

Limits of Residual Solvents

TABLE 1: CLASS 1 RESIDUAL SOLVENTS [1]

RESIDUAL SOLVENT	CONCENTRATION LIMIT (PPM)	TOXICOLOGICAL CONCERN
Benzene	2	Carcinogen
Carbon Tetrachloride	4	Toxic and Environmental Hazard
1,2-Dichloroethane	5	Toxic
1,1-Dichloroethene	8	Toxic
1,1,1-Trichloroethane	1500	Environmental Hazard

TABLE 2: CLASS 2 RESIDUAL SOLVENTS, WHERE PDE IS THE PERMITTED DAILY EXPOSURE [2]

RESIDUAL SOLVENT	PDE (MG/DAY)	CONCENTRATION LIMIT (PPM)
Acetonitrile	4.1	410
Chlorobenzene	3.6	360
Chloroform	0.6	60
Cyclohexane	38.8	3880
1,2-Dichloroethene	18.7	1870
1,2-Dimethoxyethane	1.0	100
N,N-Dimethylacetamide	10.9	1090
N,N-Dimethylformamide	8.8	880
1,4-Dioxane	3.8	380
2-Ethoxyethanol	1.6	160
Ethylene glycol	6.2	620
Formamide	2.2	220
Hexane	2.9	290
Methanol	30.0	3000
2-Methoxyethanol	0.5	50
Methylbutylketone	0.5	50
Methylcyclohexane	11.8	1180
Methylene chloride	6.0	600
N-Methylpyrrolidone	5.3	530
Nitromethane	0.5	50
Pyridine	2.0	200
Sulfolane	1.6	160
Tetrahydrofuran	7.2	720
Tetralin	1.0	100
Toluene	8.9	890
Tricholroethylene	0.8	80
Xylene	21.7	2170

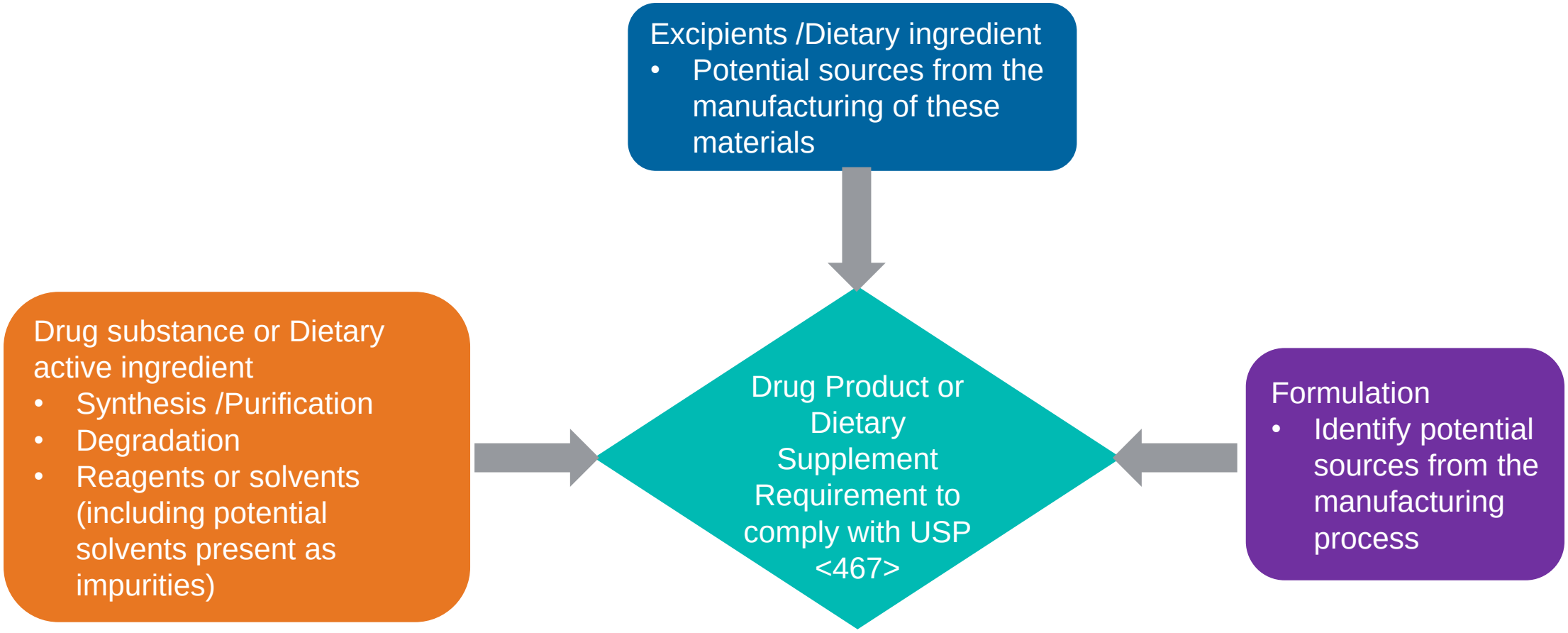
TABLE 3: CLASS 3 RESIDUAL SOLVENTS

RESIDUAL SOLVENT
Acetic acid
Acetone
Anisole
1-Butanol
2-Butanol
Butyl acetate
Tert-Butylmethyl ethe
Cumene
Dimethyl sulfoxide
Ethanol
Ethyl acetate
Ethyl ether
Ethyl formate
Formic acid
Heptane
Isobutyl acetate
Isopropyl acetate
Methyl acetate
3-Methyl-1-Butanol
Methylethylketone
Methylisobutylketone
2-Methyl-1-propanol
Pentane
1-Pentanol
1-Propanol
2-propanol
Propyl acetate

Residual solvents should be limited in drug substances, excipients, dietary ingredients, and official products because of the inherent toxicities of these residual solvents. - [467 RESIDUAL SOLVENTS (uspnf.com)]

Potential Sources of Residual Solvents to be Considered

In pharmaceutical drug products and dietary supplements



For more details: refer to 467 RESIDUAL SOLVENTS (uspnf.com)

Changes to Residual Solvents

USP <467> – Official December 2020

- Methylisobutylketone added to Class 2 list
- Methylisobutylketone used for system suitability resolution

Three new solvents to be added in next draft

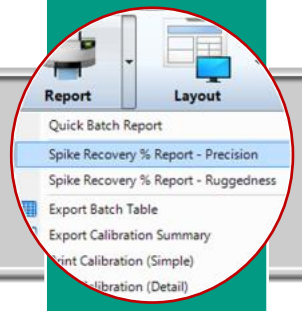
- 2-Methyltetrahydrofuran – Class 3
- Cyclopentyl methyl ether – Class 2
- Tert-butyl alcohol – Class 2

Agilent Innovative Solutions for Residual Solvent Analysis

Sample Preparation Guidance

Spares & solutions (USP/ICH calibration standards)

Easy-to-use, Robust & Reliable Instruments



Preset Methods pre-define settings & reporting tools

SOPs/start-up documentation for method set-up

Installation & Validation Services & Support

Compliant SW options, for any size and type of laboratory

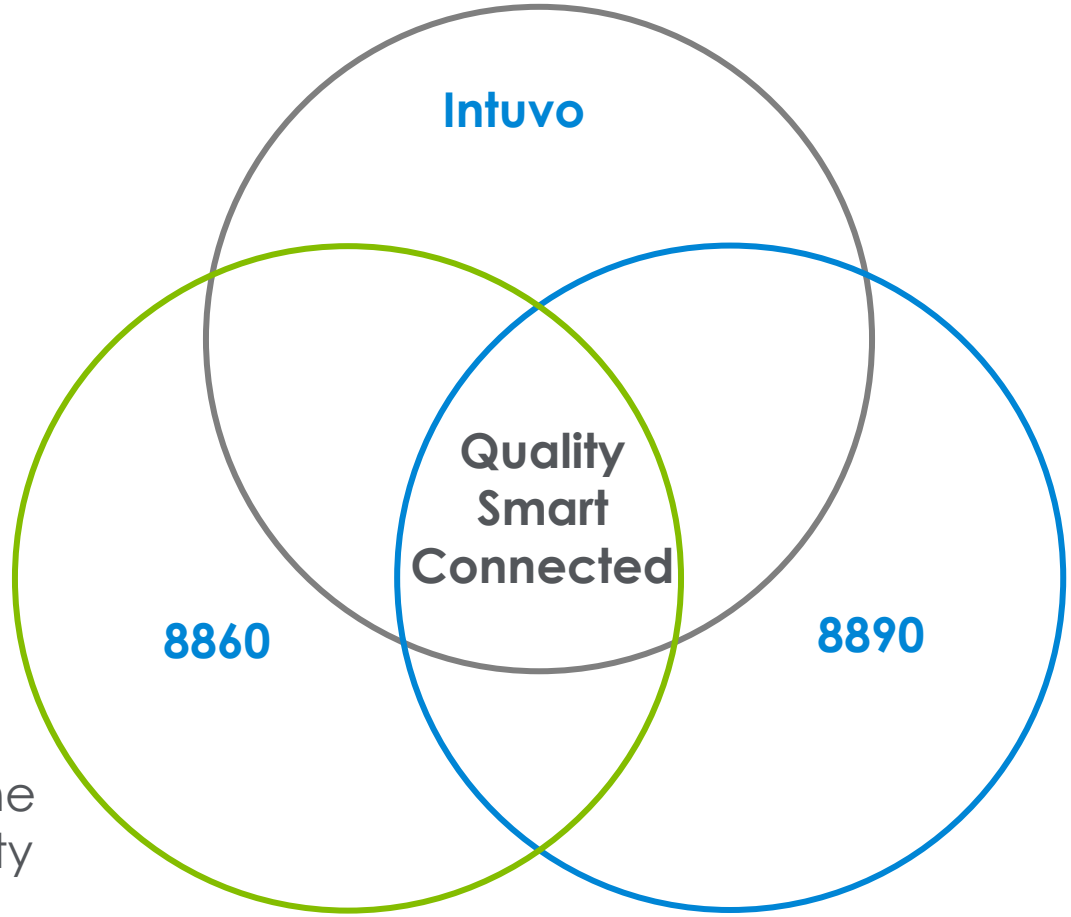
Technical expertise, training & support

A Flexible Portfolio of Products

Something for everyone!

Ultimate productivity & usability, especially for MS

Core routine applicability



Advanced flexibility & expandability

8890 Enhancements

GUI/Display/Touchscreen

- “At-GC”
  - Enhanced Diagnostics
  - Chromatographic Attributes
  - Maintenance
  - Instrument Status
  - Extensive User Info
- Capacitive touch screen

On-Board CPU → Browser UI

- GC info available via PC, Tablet, Mobile

7” Touchscreen

Column smart key and USB

… and other product design enhancements

Agilent's GC & GC/MSD for Residual Solvent Analysis

Routine Analysis → **Rapid High Throughput** → **Sensitivity**

Intuvo 9000/8697HSS

8890GC/7697HSS

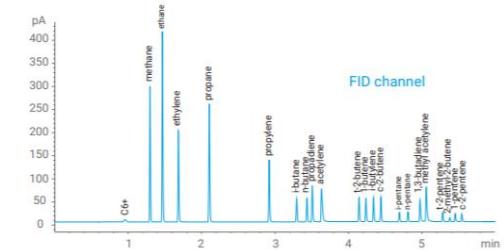
8890GC/5977MSD

All systems are equally capable of delivering all USP/ICH compliance requirements

Agilent's Residual Solvents Workflow

Which GC is right for my analysis?

Calibrate → **Separate** → **Identify** → **Analyze**



Enhanced detection and identification analysis options of analytes in a single mix -

- Splitting to two columns for dual detector analysis
- Agilent GC coupled to GC/MS System

GC System / Attributes	Intuvo 9000	8890
Performance	✓✓	✓
Detector (FID and MS)	✓✓	✓✓
Footprint	✓✓	✓
Compliant SW	✓✓	✓✓
Non-Agilent CDS	✓✓	✓✓
Direct Replacement	✓	✓✓
Revalidate SOP	✓	✓✓

Agilent GC/FID and GC/MS Workflow for Residual Solvent Analysis

Confidently identify and quantify residual solvent in APIs and drug products

Calibrate

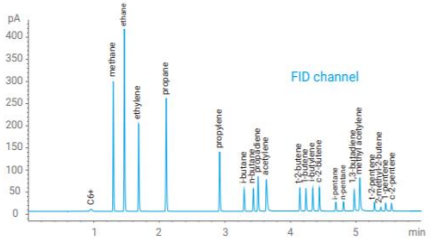
Ideal for routine & HT analysis

Separate

Identify

Intuvo 9000/8697HSS

Analyze



Quantitative Analysis of USP residual solvents even in trace levels

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Calibrate

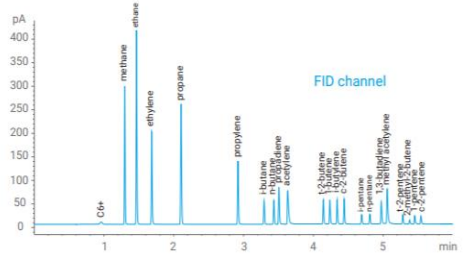
Ideal for unknown analysis

Separate

Identify

8890GC/5977MSD

Analyze



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USP <467> Residual Solvent Requirements

USP <467> specifies a single-column analysis

- A secondary analysis is performed if the solvent is found above limit detection.
- An Intuvo 9000 GC configured with an inlet split to two columns and two FIDs can perform both analyses in a single run.

USP 40, general chapter USP <467> Residual Solvents https://hmc.usp.org/sites/default/files/documents/HMC/GCs-Pdfs/c467.pdf

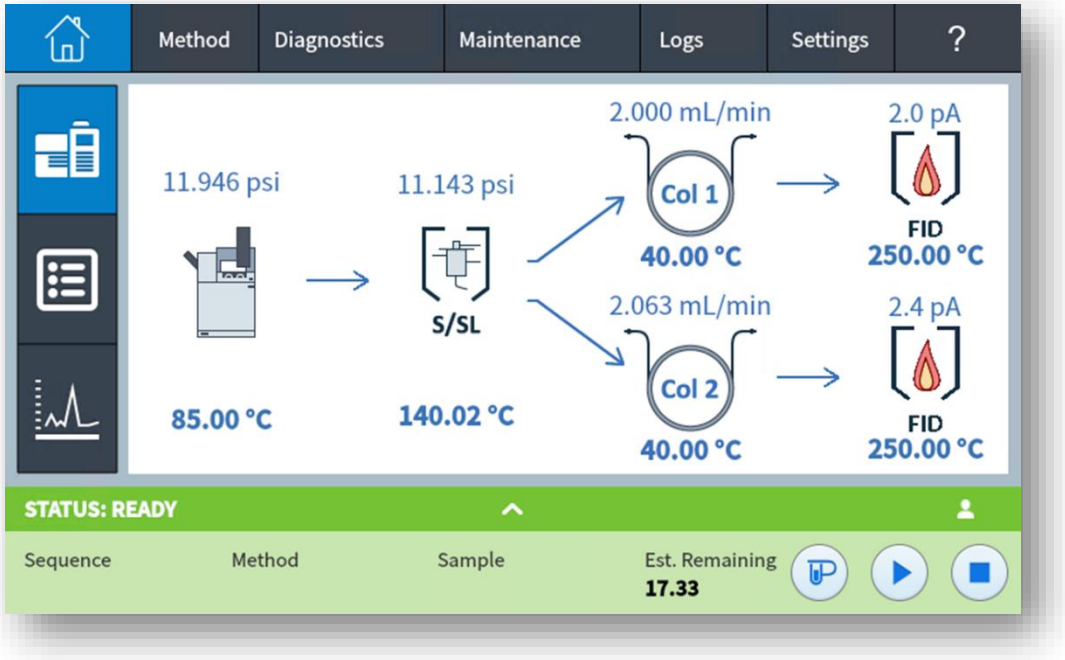
USP <467> Columns and Performance Requirements

Procedure A – Initial identification and limit test

- DB-Select 624 UI
- s/n of 1,1,1-trichloroethane > 5
- s/n of all Class 1 solvents > 3
- Resolution of acetonitrile and methylene chloride > 1

Procedure B – Secondary analysis for confirmation

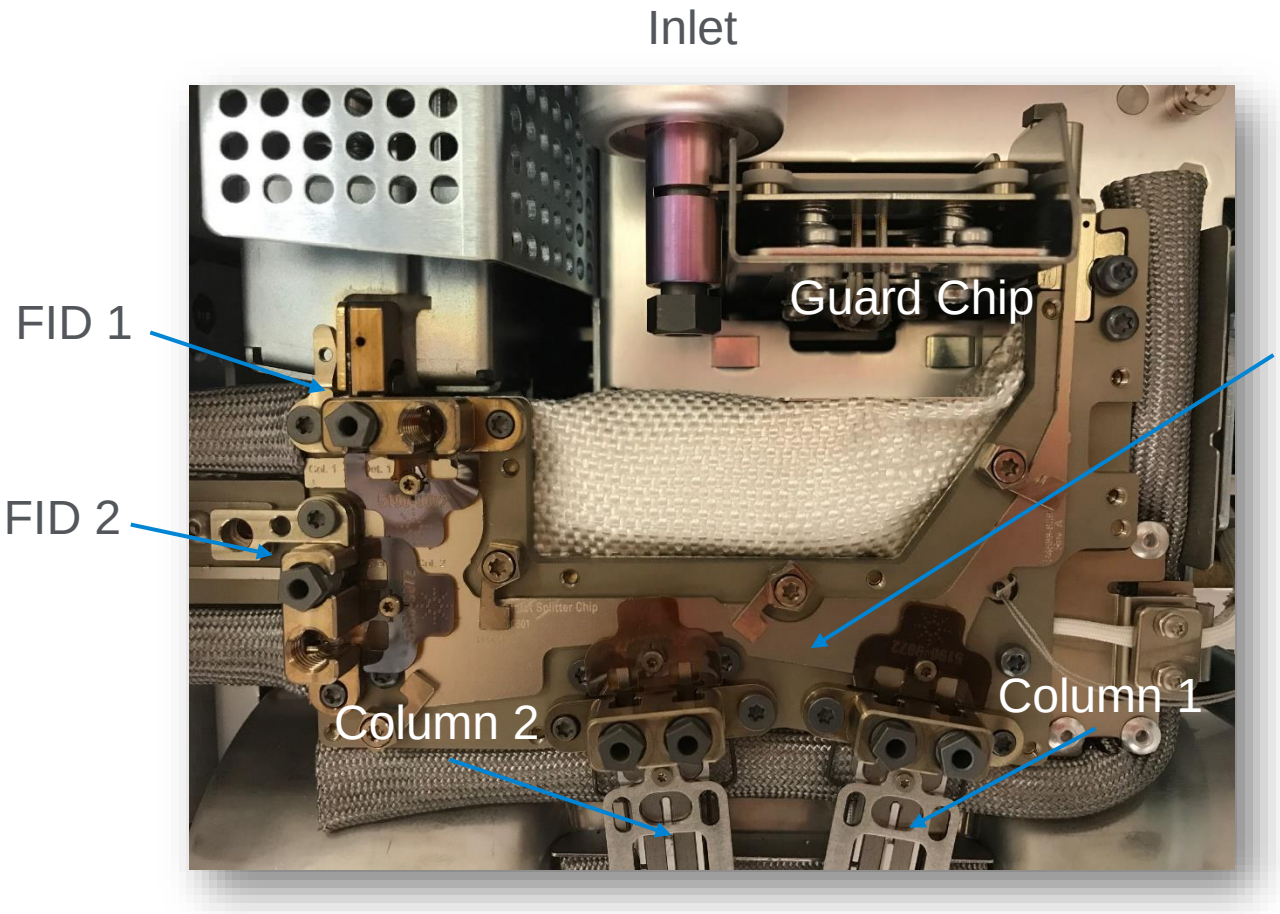
- DB-Wax Ultra Inert
- s/n of benzene > 5
- s/n of all Class 1 solvents > 3
- Resolution of **methylisobutylketone** and cis-dichloroethene > 1



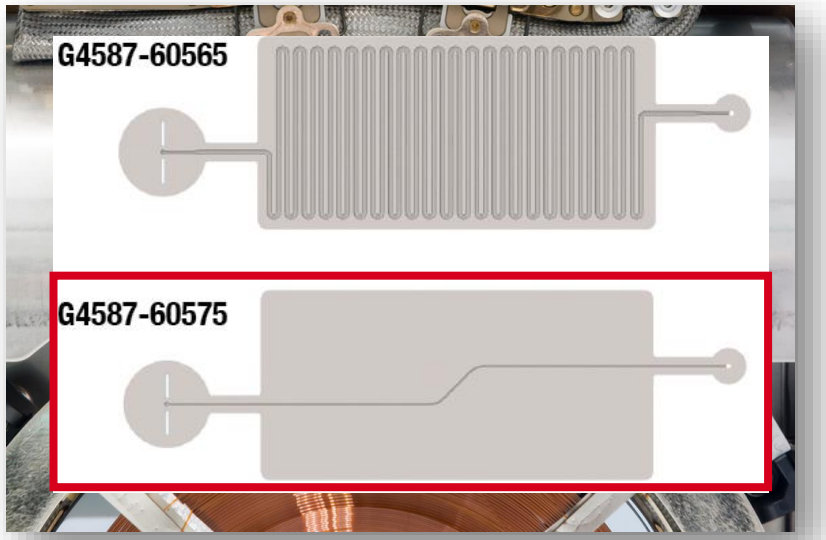
USP <467> https://www.uspnf.com/sites/default/files/usp_pdf/EN/USPNF/generalChapter467Current.pdf

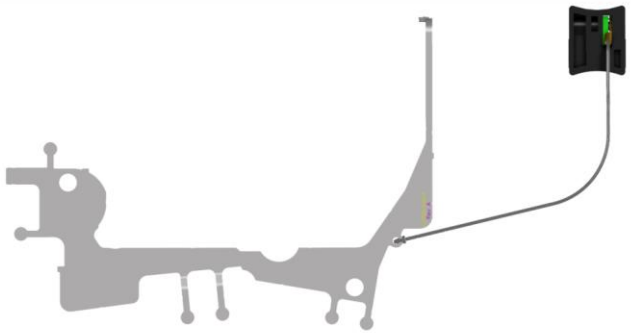
Configuration

- Headspace to SSL
- Inlet splitter flow chip – equally splits to two columns
- Two columns to two FID detectors



Inlet splitter flow chip

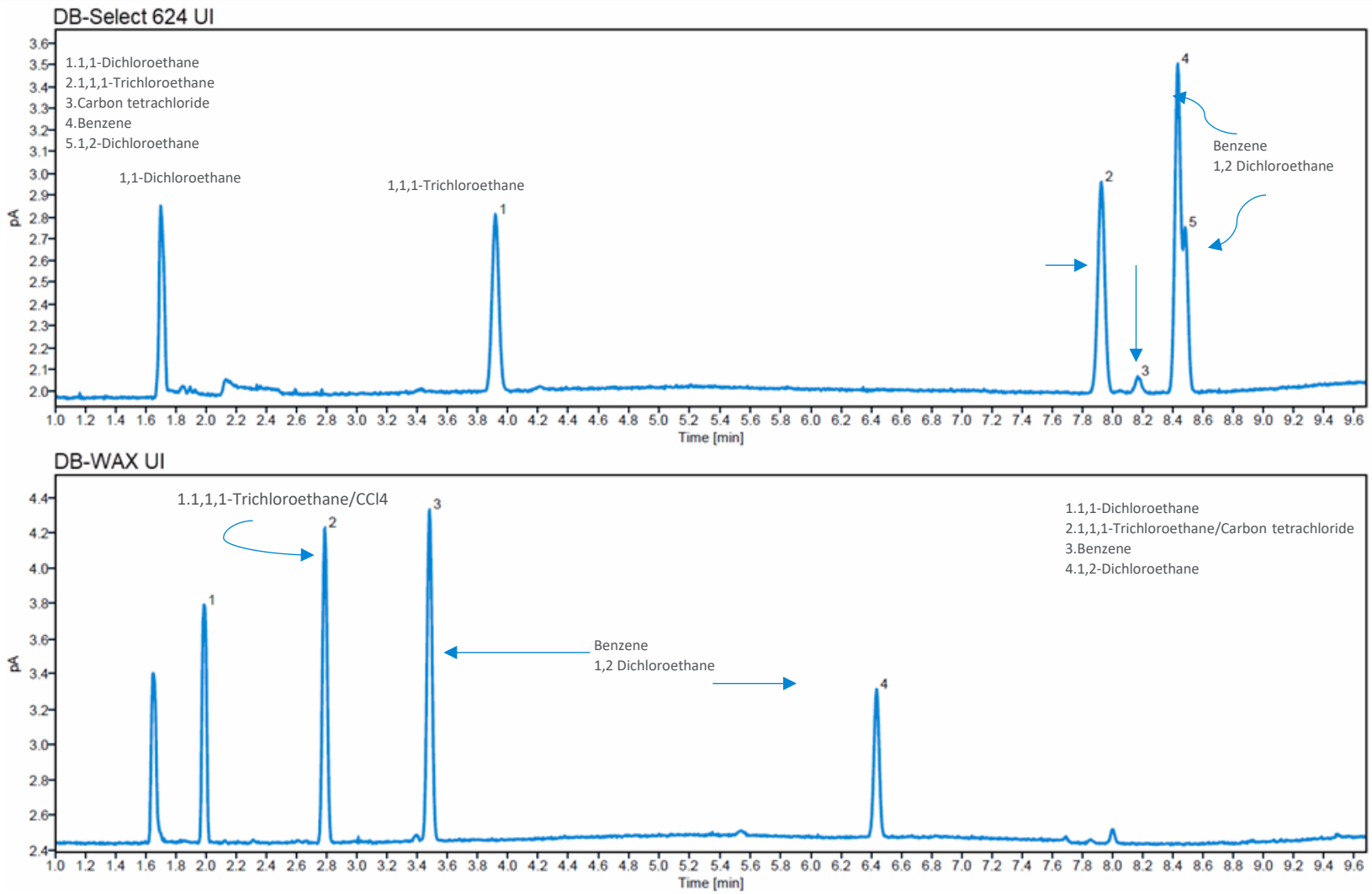




Class 1, DB-Select 624 UI & DB-WAX Ultra Inert

Signal to Noise requirements are met

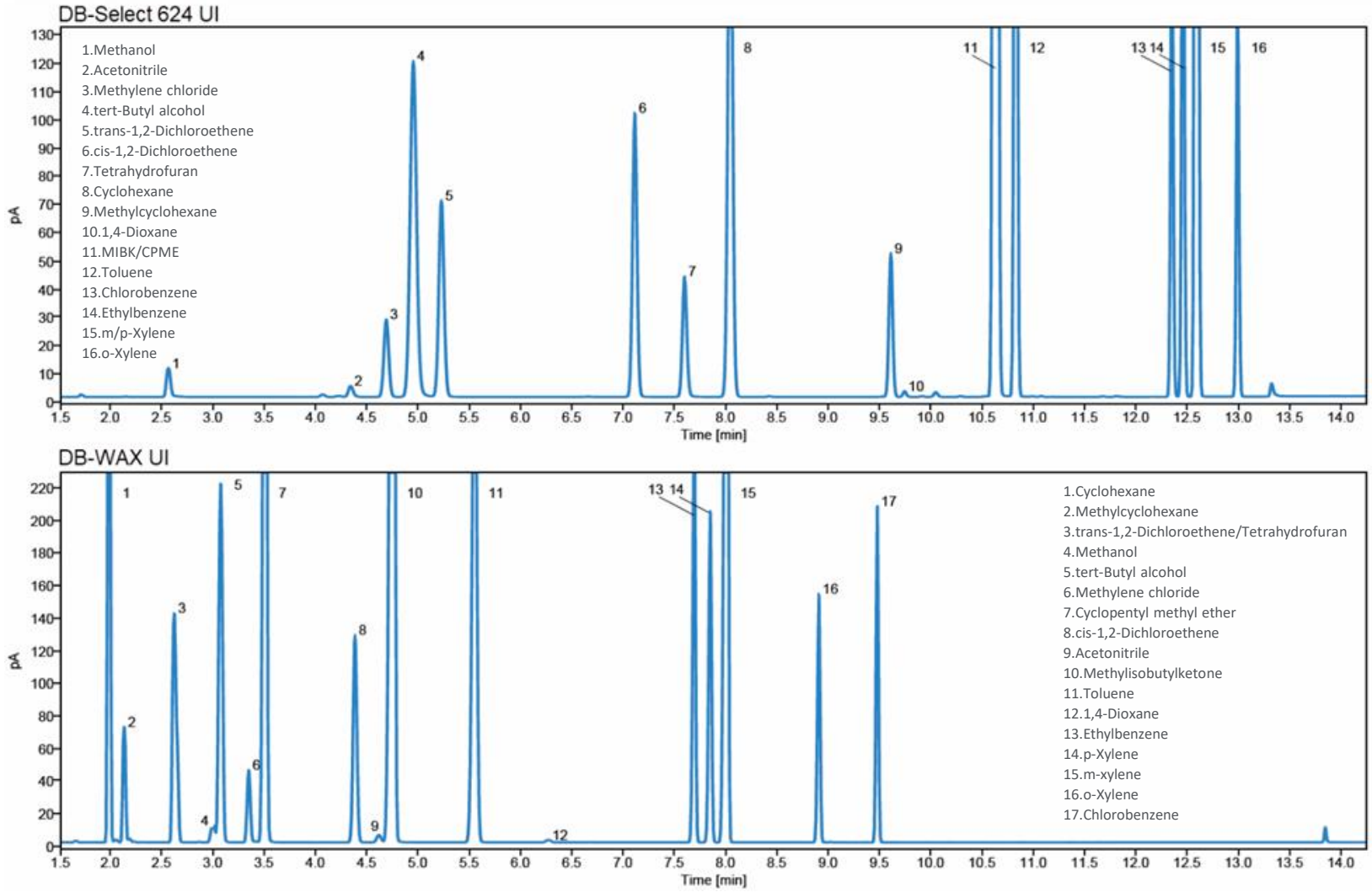
Signal to Noise requirements are met



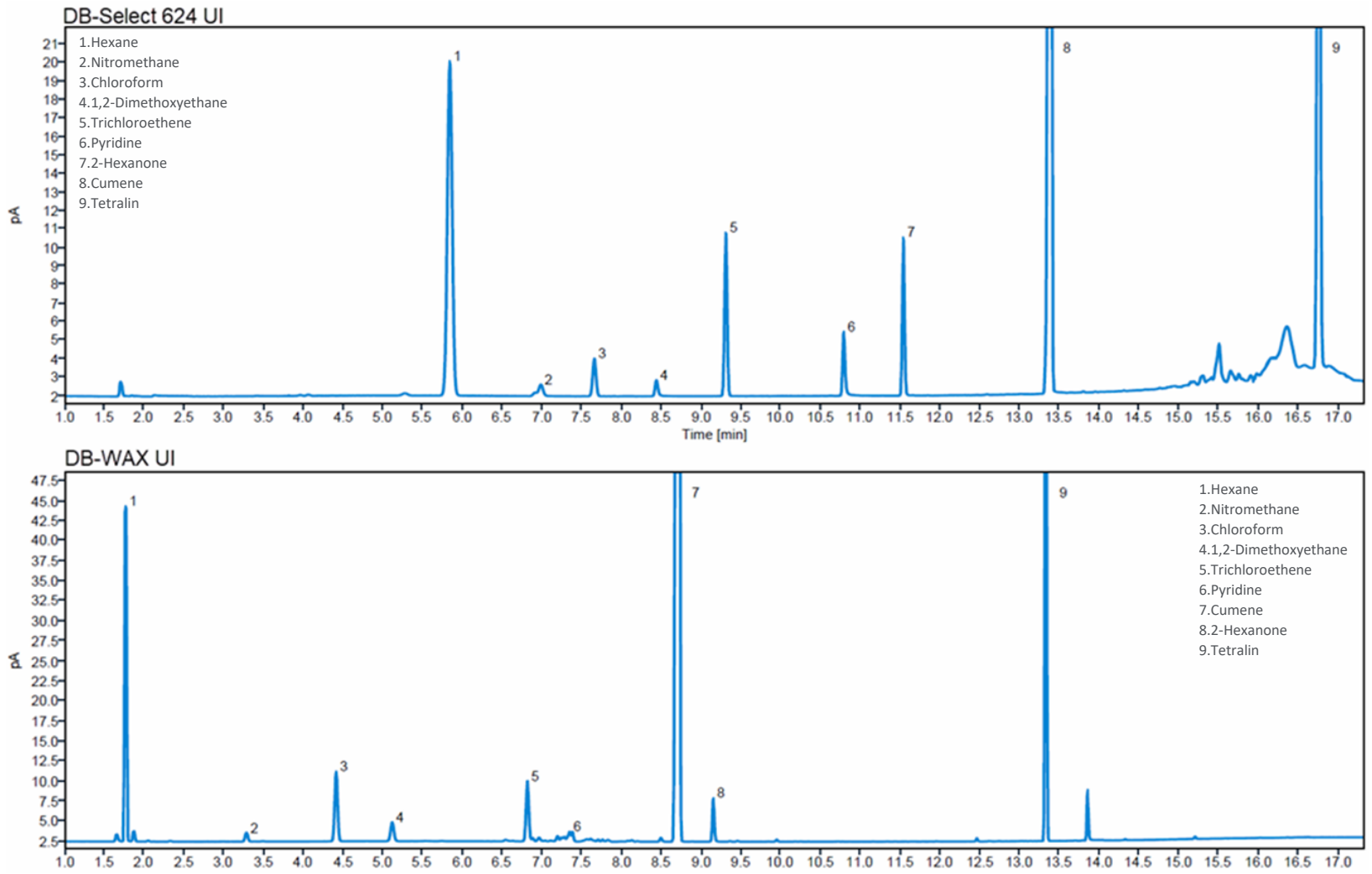
Class 2A, DB-Select 624 UI & DB-WAX Ultra Inert

Resolution > 1

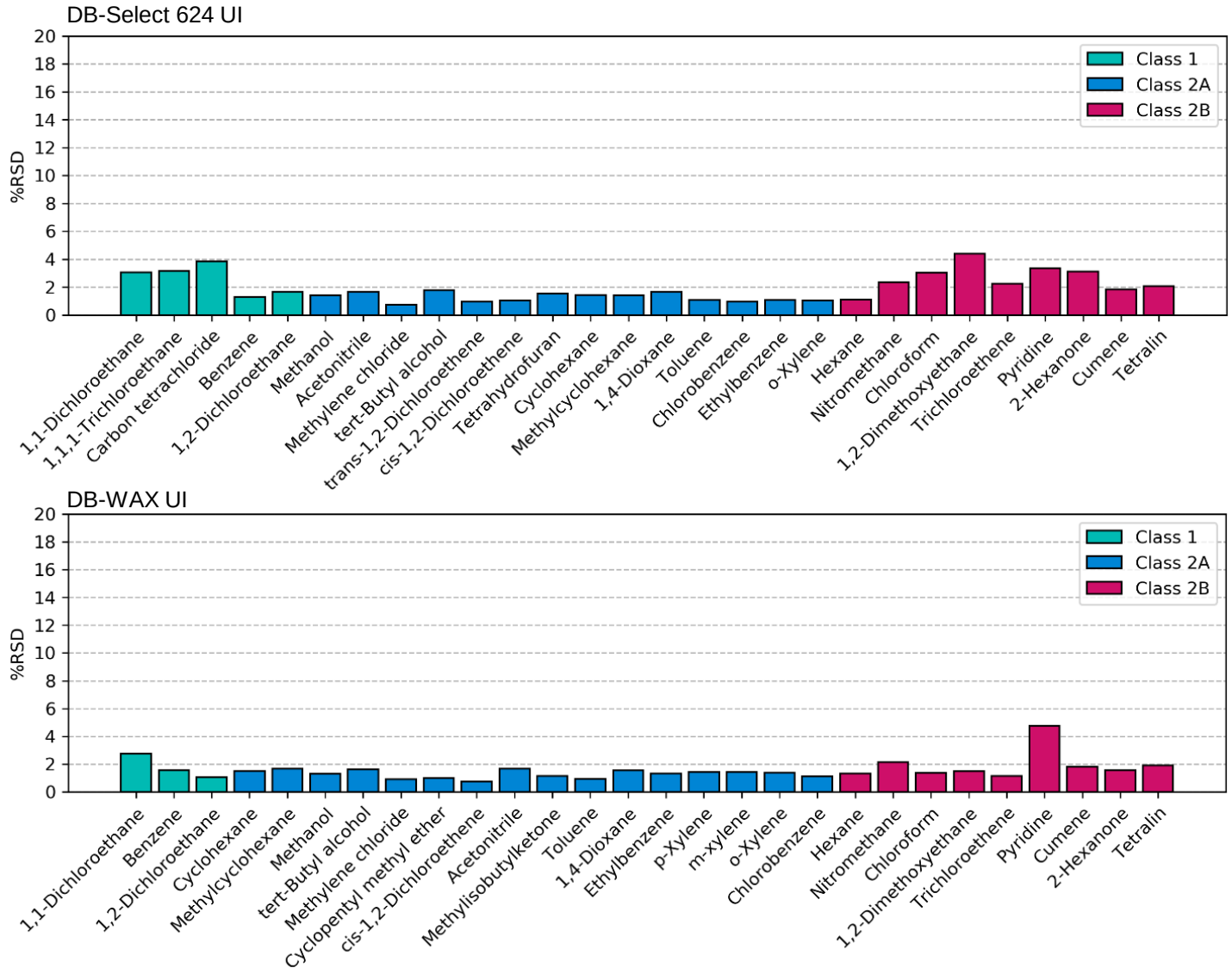
Resolution > 1



Class 2B, DB-Select 624 UI & DB-WAX Ultra Inert



Repeatability (n=10)



USP Method Parameter Comparison for the Agilent 8697 and 7697A Headspace Samplers

Conceptually, both 8897 and 7697A HSSs are very similar, the 8697 HSS can operate with the same method parameters as the 7697A.

Headspace parameters for the USP residual solvents method are shown as an example.

HS Parameter	GC/HS			
	7890/7697A	9000/7697A	8890/7697A	9000/8697
Sample Loop Volume	1 mL	1 mL	1 mL	1 mL
Oven Temperature	85 °C	85 °C	85 °C	85 °C
Loop Temperature	85 °C	85 °C	85 °C	85 °C
Transfer Line Temperature	100 °C	100 °C	100 °C	100 °C
Vial Equilibration Time	40 min	40 min	40 min	40 min
Injection Duration	0.5 min	0.5 min	0.5 min	0.5 min
Vial Size	10 mL	10 mL	10 mL	20 mL*
Vial Shaking	On, Level 2	On, Level 2	On, Level 2	On, Level 2
Vial Fill Mode	Flow to pressure	Flow to pressure	Flow to pressure	Flow to pressure
Vial Fill Flow	50 mL/min	50 mL/min	50 mL/min	50 mL/min
Vial Fill Pressure	15 psi	15 psi	15 psi	15 psi
Loop Ramp Rate	20 psi/min	20 psi/min	20 psi/min	20 psi/min
Final Loop Pressure	0 psi	0 psi	0 psi	4 psi*
Loop Equilibration Time	0.05 min	0.05 min	0.05 min	0.05 min

* The most recent application note used 20 mL vials to better accommodate a 6 mL sample volume. Also, the final loop pressure was increased to 4 psi to reduce the potential impact of atmospheric pressure variations, but 0 psi can be used without issue.

Analysis of Three Classes of Residual Solvents in USP <467> and Chinese Pharmacopoeia by using GC/FID/MSD System

Agilent

Configuration Highlights

- This application covers three classes of solvents with a total of up to 62 compounds.
- A purged two-way CFT device was used to split the column effluent 1:1 to the MSD and FID.
- When unknown peaks or unknown solvents appear, this system is the best solution for solvent identification and quantification
- Both MSD and FID signals can be used for quantitative analysis, MSD is a good quantitative supplement for compounds with poor resolution, while FID can expand the linear range.

Compounds List

The list of compounds in USP <467> and Chinese pharmacopoeia is almost the same.

Class 1

Table 1. Class 1 Residual Solvents
(Solvents that should be avoided)

Solvent	Concentration Limit (ppm)
Benzene	2
Carbon tetrachloride	4
1,2-Dichloroethane	5
1,1-Dichloroethene	8
1,1,1-Trichloroethane	1500

Class 3

Table 3. Class 3 Residual Solvents
(limited by GMP or other quality-based requirements in drug substances, excipients, and drug products)

Acetic acid	Heptane
Acetone	Isobutyl acetate
Anisole	Isopropyl acetate
1-Butanol	Methyl acetate
2-Butanol	3-Methyl-1-butanol
Butyl acetate	Methylethylketone
tert-Butylmethyl ether	Methylisobutylketone
Cumene	2-Methyl-l-propanol
Dimethyl sulfoxide	Pentane
Ethanol	1-Pentanol
Ethyl acetate	1-Propanol
Ethyl ether	2-Propanol
Ethyl formate	Propyl acetate
Formic acid	

Class 2

Table 2. Class 2 Residual Solvents

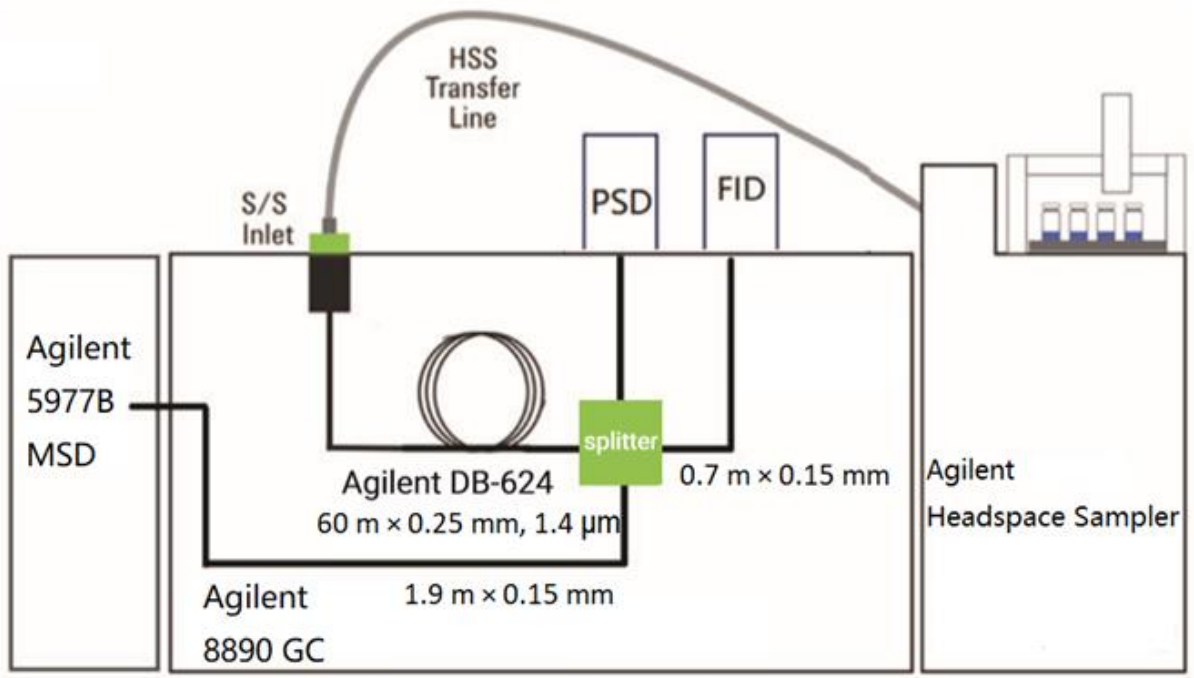
Solvent	PDE (mg/day)
Acetonitrile	4.1
Chlorobenzene	3.6
Chloroform	0.6
Cumene	0.7
Cyclohexane	38.8
1,2-Dichloroethene	18.7
1,2-Dimethoxyethane	1.0
N,N-Dimethylacetamide	10.9
N,N-Dimethylformamide	8.8
1,4-Dioxane	3.8
2-Ethoxyethanol	1.6
Ethylene glycol	6.2
Formamide	2.2
Hexane	2.9
Methanol	30.0
2-Methoxyethanol	0.5
Methylbutylketone	0.5
Methylcyclohexane	11.8
Methylene chloride	6.0
N-Methylpyrrolidone	5.3
Nitromethane	0.5
Pyridine	2.0
Sulfolane	1.6
Tetrahydrofuran	7.2
Tetralin	1.0
Toluene	8.9
Trichloroethylene	0.8
Xylene*	21.7

Red: liquid injection

Others: headspace injection

Headspace Injection

Instrument conditions



Agilent 8890 GC	
Parameter	Value
Inlet	SSL, 250 °C, split 10:1
Liner	Straight, deactivated, 2 mm ID (part number 5181-8818)
CFT Device	Purged 2-way splitter Split Ratio 1:1 MSD:FID
PSD	3.8 psi constant pressure
Column	Agilent DB-624 60 m × 0.25 mm, 1.4 µm (part number 122-1364)
Carrier	Helium, 1 mL/min, constant flow
FID Restrictor	0.7 m × 0.15 mm id deactivated fused silica tubing
MSD Restrictor	1.9 m × 0.15 mm id deactivated fused silica tubing
Oven	40 °C (10 min), then 5 °C/min to 80 °C, then 12 °C/min to 220 °C (10 min)
FID	Temperature: 250 °C Hydrogen: 30 mL/min Air: 300 mL/min Make -up gas (N2):25 mL/min
Transfer line temperature	250 °C
Agilent 5977B GC/MSD	
Parameter	Value
Ionization type	EI
Source temperature	230 °C
Quad temperature	150 °C
Drawout plate	3 mm
Tune file	Atune.u
Acquisition type	Scan
Solvent delay	6 min
Relative Voltage	0

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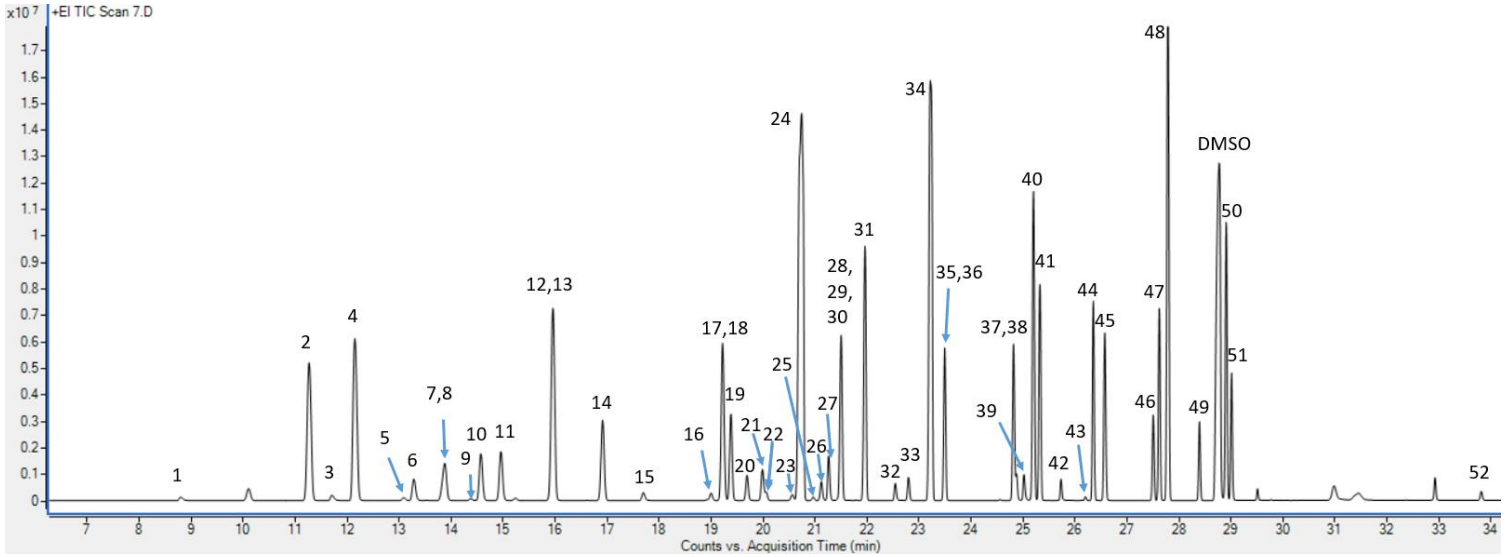
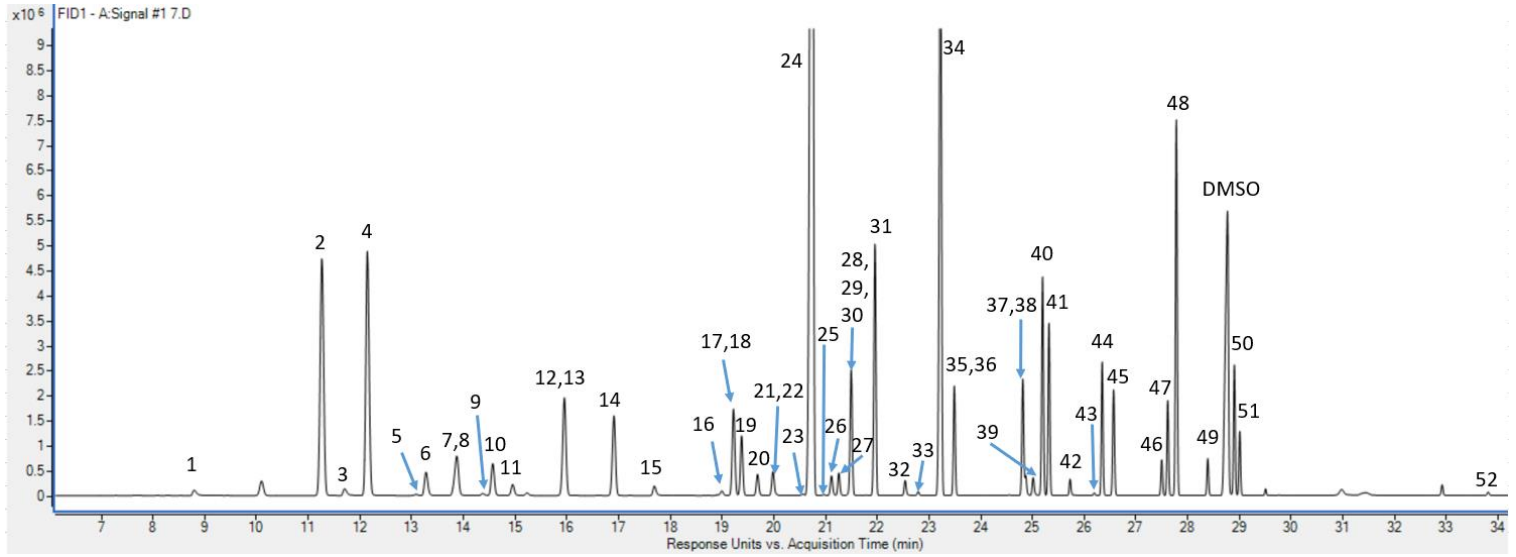
Headspace Injection



MSD scan



FID

Headspace Injection

Results of the 52 compounds

No.	Name	RT	m/z	Linearity range(µg/mL)	MSD R2	FID R2	Area RSD% L4 (n=8)	MDL (MSD) µg/mL L2 (n=8)
1	Methanol	8.818	31	0.75-150	0.9998	0.9994	2.2	0.194
2	Pentane	11.251	43	0.5-100	0.9944	0.9997	2	0.1428
3	Ethanol	11.73	31	2-100	0.9999	0.9998	1.2	0.5137
4	Ethyl ether	12.142	74.1	0.5-100	0.9911	0.9998	4.3	0.1469
5	1,1-Dichloroethene	13.083	61	0.004-0.8	0.9997	0.9986	1.7	0.0028
6	Acetone	13.283	43	0.5-100	0.9999	0.9996	2.1	0.2265
7	Isopropanol	13.854	45	0.5-100	0.9997	0.9979	2.9	0.2446
8	Ethyl formate	13.873	45	0.5-100			4.3	0.2449
9	Acetonitrile	14.39	41	0.1-20	0.9996	0.9984	4.2	0.0319
10	Methyl acetate	14.564	43	0.5-100	0.9998	0.9998	2.7	0.4236
11	Methylene chloride	14.947	84	0.15-30	0.9997	0.9997	2.1	0.0326
12	2-Methoxy-2-methylpropane	15.938	73	0.1-20	0.9988	0.9998	2.1	0.0352
13	trans-1,2-Dichloroethene	15.979	95.9	0.235-47	0.9969	0.9998	1.7	0.065
14	Hexane	16.899	57	0.1-20	0.9995	0.9998	2.2	0.0739
15	1-Propanol	17.712	31	0.5-100	0.9995	0.9996	2	0.1799
16	Nitromethane	19	46	0.5-100	0.9999	0.9991	1.9	0.2521
17	cis-1,2-Dichloroethene	19.21	96	0.235-47	0.9988	0.9999	2.5	0.0447
18	2-Butanone	19.225	43	0.5-100	0.998	0.9999	2.3	0.1471
19	Ethyl acetate	19.375	43	0.5-100	0.9986	0.9997	1.4	0.3054
20	2-Butanol	19.688	45	0.5-100	0.9998	0.9999	2.4	0.2371
21	Tetrahydrofuran	19.985	42	0.18-36	0.9998	0.9998	2.1	0.0532
22	Chloroform	20.054	83	0.015-3	0.9997		1.6	0.0058
23	1,1,1-Trichloroethane	20.546	97	0.005-1	0.9999	0.9998	1.3	0.0025
24	Cyclohexane	20.707	84	1.0-49 (195)*	0.9908	0.9997	1.8	0.188
25	Carbon tetrachloride	20.962	117	0.002-0.4	0.9998	0.9992	2.8	0.002

No.	Name	RT	m/z	Linearity range(µg/mL)	MSD R2	FID R2	Area RSD% L4 (n=8)	MDL (MSD) µg/mL L2 (n=8)
27	1,2-Dimethoxyethane	21.265	45	0.5-100	0.9999	0.9995	1	0.2561
28	Benzene	21.442	78	0.001-0.2	0.9995	0.9998	5.8	0.0008
29	1,2-Dichloroethane	21.442	62	0.01-0.5	0.9989		1.5	0.0016
30	Isopropyl acetate	21.496	61	0.5-100	0.9985	0.9998	0.8	0.1636
31	Heptane	21.956	71	0.1-20	0.9974	0.9996	2.4	0.0343
32	1-Butanol	22.547	56	0.5-100	0.9994	0.9998	2.4	0.1717
33	Trichloroethylene	22.791	130	0.015-3	0.9999	0.9999	1.8	0.0065
34	Methyl cyclohexane	23.208	83	0.3-15 (59)*	0.9989	0.9997	2.3	0.0722
35	1,4-Dioxane	23.489	88	0.095-19	0.9999	0.9999	3.3	0.0549
36	Propyl acetate	23.491	43	0.5-100	0.9966		3	0.2675
37	4-Methyl-2-pentanone	24.815	43	0.5-100	0.9985	0.9999	2.2	0.1429
38	Isoamyl alcohol	24.879	55.1	0.5-100	0.9991	0.9996	2.4	0.2562
39	Pyridine	25.024	79	2-100	0.9992	0.9997	2.1	0.5016
40	Toluene	25.196	91	0.225-22 (44)*	0.9964	0.9998	2.1	0.0651
41	Isobutyl acetate	25.322	56	0.5-100	0.9958	0.9999	2.1	0.1784
42	1-Pentanol	25.735	42	0.5-100	0.9996	0.9998	2.1	0.3319
43	2-Hexanone	26.201	58	0.06-3	0.9995	0.9998	2.1	0.0107
44	Butyl acetate	26.351	43	0.5-100	0.9957	0.9999	2.3	0.2502
45	Tetrahydrothiophene	26.571	88	0.5-100	0.9996	0.9999	1.4	0.18
46	Chlorobenzene	27.503	112	0.09-18	0.9999	0.9997	2.5	0.0215
47	Ethylbenzene	27.618	91	0.09-18	0.9986	0.9997	4.1	0.0288
48	m,p-xylene	27.782	106	0.4-40 (80)*	0.9963	0.9997	3.3	0.1074
49	o-xylene	28.393	91	0.05-10	0.9999	0.9996	2.6	0.0173
50	Isopropylbenzene	28.904	105	0.1-20	0.9983	0.9996	2.4	0.0391
51	Anisole	29.011	108	0.5-100	0.9999	0.9997	2.8	0.1892
52	1,2,3,4-Tetrahydronaphthalene	33.814	104	0.015-3	0.9998	0.9993	2	0.0045

Liquid Injection

Compounds list in liquid injection

2-Methoxyethanol

2-Ethoxyethanol

N,N-dimethylformamide

N,N-dimethylacetamide

Acetic acid

Formic acid

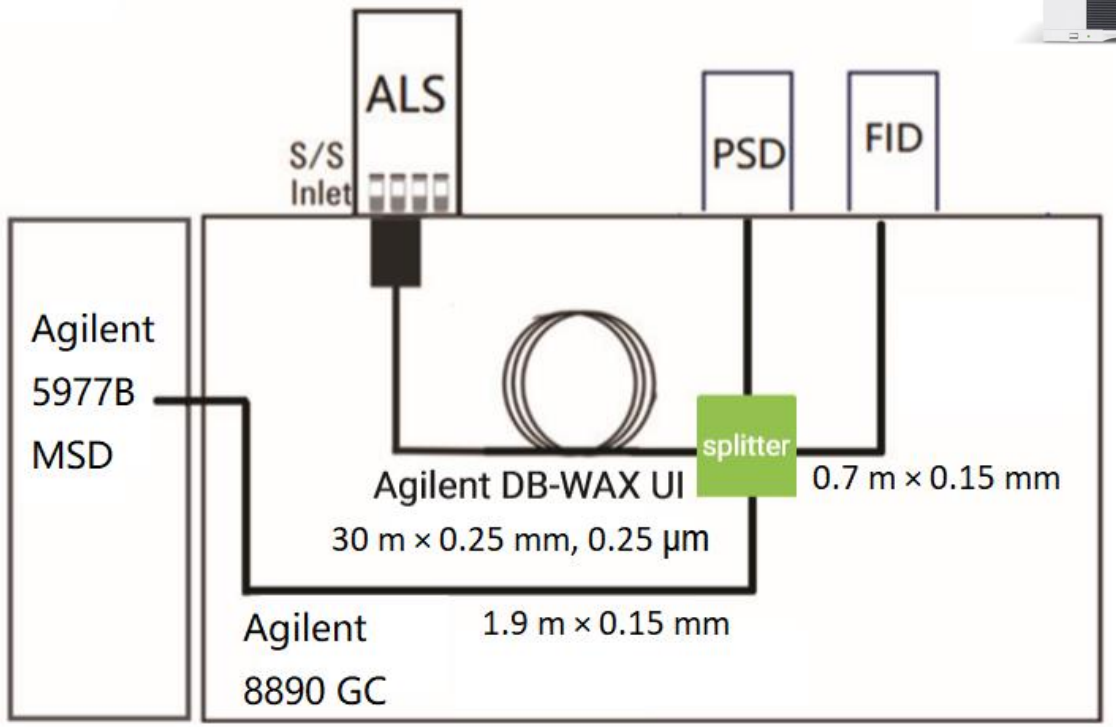
Ethylene glycol

N-methylpyrrolidone

Formamide

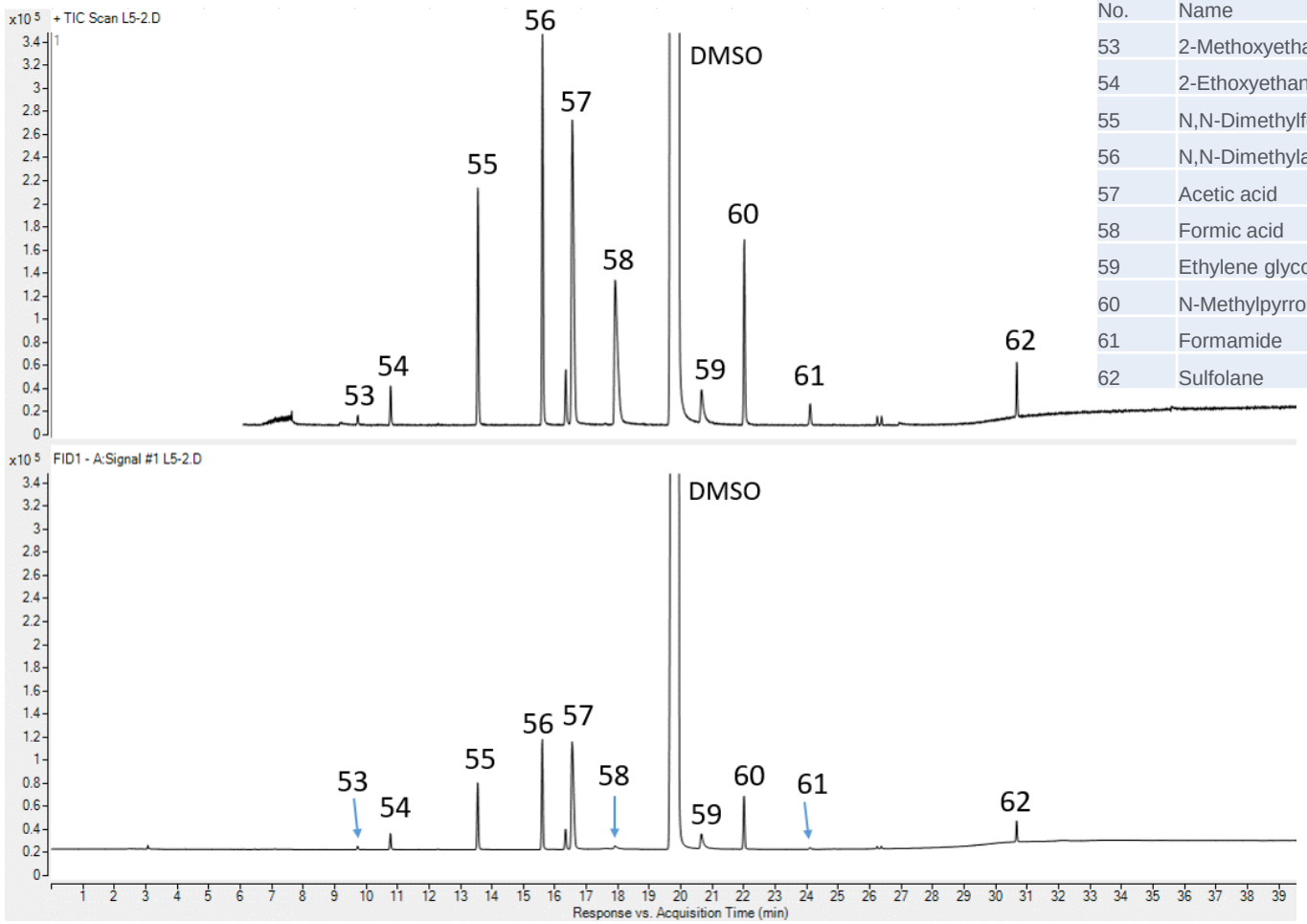
Sulfolane

Instrument configuration



Standards: USP 467 Class 2C (Agilent p/n: 5190-0493)
acetic acid (99.8%, purity), formic acid (98%, purity)

Liquid Injection



No.	Name
53	2-Methoxyethanol
54	2-Ethoxyethanol
55	N,N-Dimethylformamide
56	N,N-Dimethylacetamide
57	Acetic acid
58	Formic acid
59	Ethylene glycol
60	N-Methylpyrrolidone
61	Formamide
62	Sulfolane

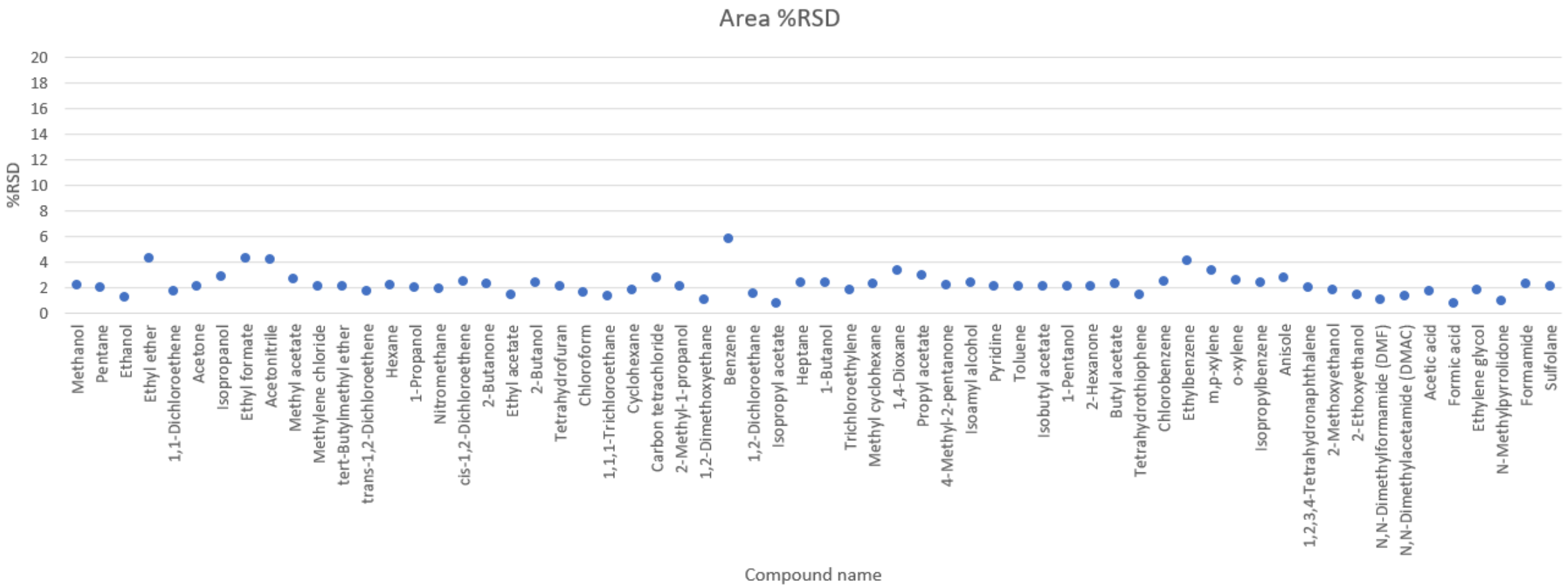
Agilent 8890 GC	
Parameter	Value
Inlet	SSL, 250 °C, split 30:1
Liner	Ultra Inert, split, low pressure drop, glass wool (p/n: 5190-2295)
Injection volume	0.5 uL
CFT Device	Purged 2-way splitter Split Ratio 1:1 MSD:FID
PSD	3.8 psi constant pressure
Column	Agilent DB-wax UI 30 m × 0.25 mm, 0.25 µm (part number 122-7032UI)
Carrier	Helium, 1 mL/min, constant flow
FID Restrictor	0.7 m × 0.15 mm id deactivated fused silica tubing
MSD Restrictor	1.9 m × 0.15 mm id deactivated fused silica tubing
Oven	40 °C, then 5 °C/min to 160 °C, then 10 °C/min to 220 °C (10 min)
FID	Temperature: 250 °C Hydrogen: 30 mL/min Air: 300 mL/min Make -up gas (N2):25 mL/min
Transfer line temperature	250 °C
Agilent 5977B GC/MSD	
Parameter	Value
Ionization type	EI
Source temperature	230 °C
Quad temperature	150 °C
Drawout plate	3 mm
Tune file	Atune.u
Acquisition type	Scan
Solvent delay	6 min
Relative Voltage	0

Liquid Injection

Results of the 10 compounds

No.	Name	RT	m/z	Linearity range µg/mL	R^2		Area RSD% L4 (n=8)	MDL (MSD) µg/mL
					MSD	FID		
53	2-Methoxyethanol	9.783	45	5-50	0.9984	0.9995	1.8	0.68
54	2-Ethoxyethanol	10.816	59	16-161	0.9973	0.9987	1.4	1.93
55	N,N-Dimethylformamide (DMF)	13.607	73	88.3-883	0.9997	0.9999	1	2.19
56	N,N-Dimethylacetamide (DMAC)	15.667	87	109.4-1094	0.9997	0.9996	1.3	2.58
57	Acetic acid	16.493	60	400-3000	0.9984	0.9997	1.7	90.12
58	Formic acid	17.774	46	400-3000	0.9995	0.9939	0.8	120
59	Ethylene glycol	20.652	31	62.2-622	0.9983	0.9982	1.8	4.44
60	N-Methylpyrrolidone	22.074	98	53-530	0.9995	0.9997	0.9	3.02
61	Formamide	24.157	45	22-221	0.9992	0.9986	2.3	2.11
62	Sulfolane	30.706	120	16-160	0.9994	0.9997	2.1	1.33

Repeatability (n=8) for 62 Compounds



Summary

- Residual solvents of Class 1, 2, and 3 were tested using the Agilent 8890 GC/FID/MSD system.
- For new drug development and quality control, FID and MSD dual-channel configurations can be powerful tools for solvent residue analysis.
- MSD analysis can avoid the uncertainty of more than 60 solvents involved in drug production.
- When unknown peaks or unknown solvents appear, this system is the best solution for solvent identification and quantification

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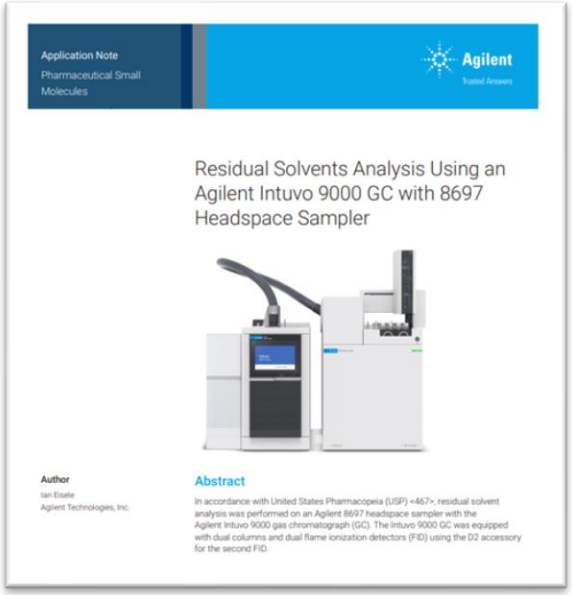
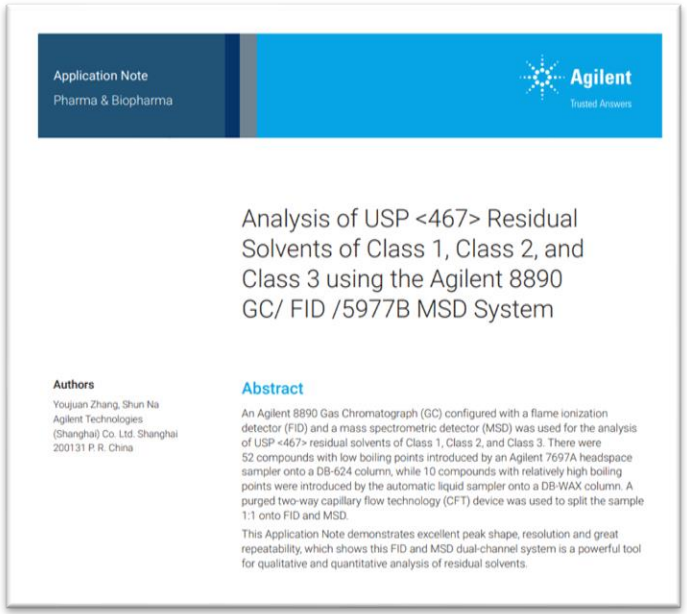
Application Notes

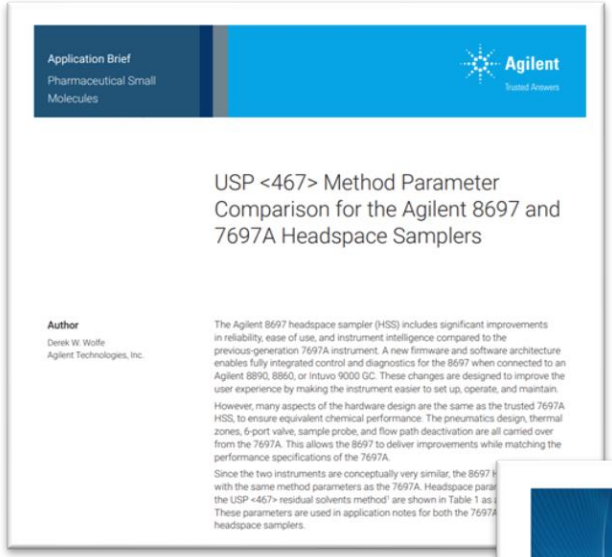


[Residual Solvents Analysis Using an Agilent Intuvo 9000 GC with 8697 Headspace Sampler]



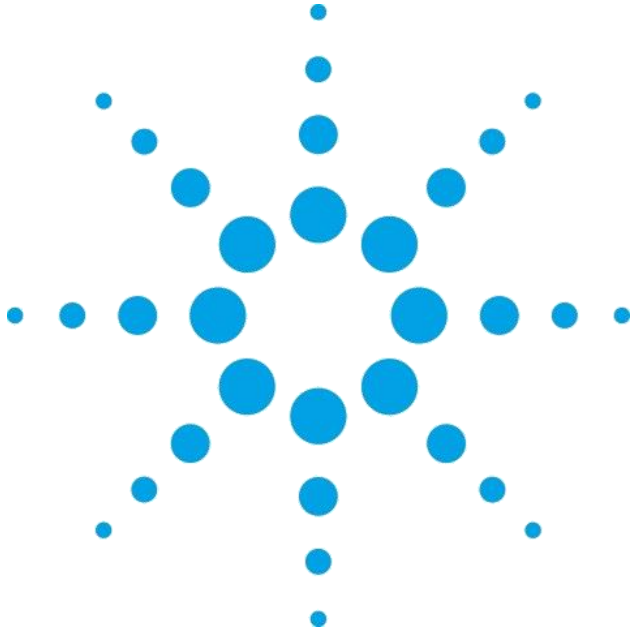
[Analysis of USP <467> Residual Solvents of Class 1, Class 2, and Class 3 using the Agilent 8890 GC/ FID /5977B MSD System]

Application Brief



[USP <467> Method Parameter Comparison for the Agilent 8697 and 7697A Headspace Samplers]

[https://www.agilent.com/cs/library/applications/5991-8032EN.pdf]



Thank you for your attention!