USP <467>

Residual solvent determination in pharmaceutical products.

PRESENTED BY

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US Pharmacopeia (USP) method <467>

- Residual solvents in pharmaceuticals are trace level impurities of Volatile Organic Compounds in **final products** or **excipients.**

- Residual solvents originate from manufacturing **processes** related to the preparation of drug products. They can also form during product **packaging** and **storage.**

- **US Pharmacopeia (USP) method <467>** delineates the procedure to identify and quantify any residual solvent present in pharmaceuticals and excipients as a result of the production process.

Classification of Residual Solvents

The USP 467 method sets the concentration limit for each solvent and describes the analysis of 53 solvents grouped according to their health hazards:

Class 1 : Solvents to be Avoided

- Known human carcinogens
- Strongly suspected human carcinogens
- Environmental hazards

Class 1 Residual Solvent		
Solvent	Concentration Limit (ppm)	Concern
Benzene	2	Carcinogen
Carbon tetrachloride	4	Toxic and environment hazard
1,2-Dichloroethane	5	Toxic
1,1-Dichloroethane	8	Toxic
1,1,1-Trichloroethane	1500	Environment hazard

Classification of Residual Solvents

Class 2 : Solvents to be Limited

- Nongenotoxic animal carcinogens or possible causative agents of other irreversible toxicity, such as neurotoxicity or teratogenicity.
- Solvents suspected of other significant but reversible toxicities.

Class 2 Residual Solvent		
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
Dichloromethane	6.0	600
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
Ethyleneglycol	6.2	620
Formamide	2.2	220
Hexane	2.9	290

Class 2 Residual Solvent		
Solvent	PDE (mg/Day)	Concentration Limit (ppm)
Methanol	30.0	3000
2-Methoxyethanol	0.5	50
Methylbutyl ketone	0.5	50
Methylcyclohexane	11.8	1180
N-Methylpyrrolidone	15.3	530
Nitromethane	0.5	50
Pyridine	2.0	200
Sulfolane	1.6	160
Tetrahydrofuran	27.2	720
Tetralin	1.0	100
Toluene	8.9	890
1,1,2-Trichloroethene	0.8	80
Xylenes	21.7	2170

Classification of Residual Solvents

Class 3 Solvents with low toxic potential

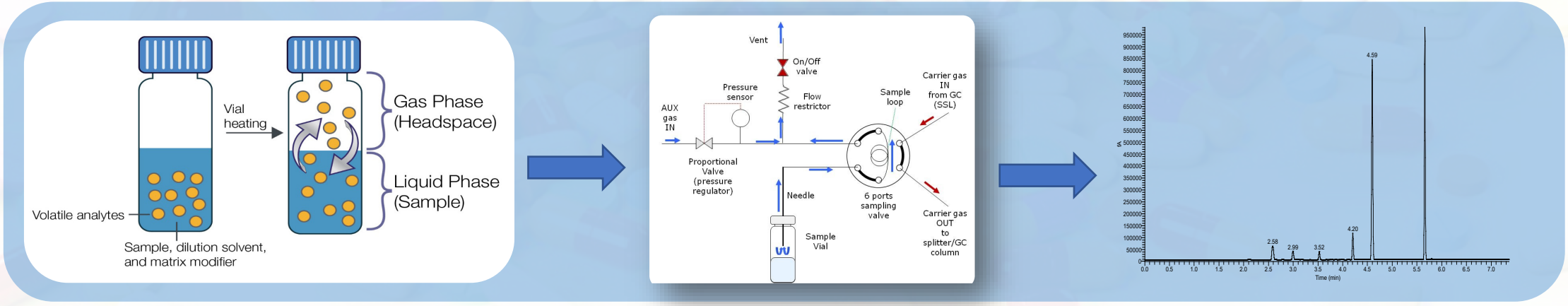
- Solvents with low toxic potential to humans; no health-based exposure limit is needed. [NOTE—Class 3 residual solvents may have PDEs of up to 50 mg or more per day.])

Class 3 Residual Solvent	
Solvent	Solvent
Acetic acid	Heptane
Acetone	Isobutyl acetate
Anisole	Isopropyl acetate
1-Butanol	Methyl acetate
2-Butanol	3-Methyl-1-butanol
Butyl acetate	Methylethyl ketone
tert-Butylmethyl ether	Methylisobutyl ketone
Cumene	2-Methyl-1-propanol
Dimethyl sulfoxide	Pentane
Ethanol	1-Pentanol
Ethyl acetate	1-Propanol
Ethyl ether	2-Propanol
Ethyl formate	Propyl acetate

Identification, Control and Quantification

Instrument

- Gas chromatography (GC)
- Headspace (HS) Sampler
- Flame ionization detection (FID)
- Mass Spectrometry (MS) detector (*Optionally*)

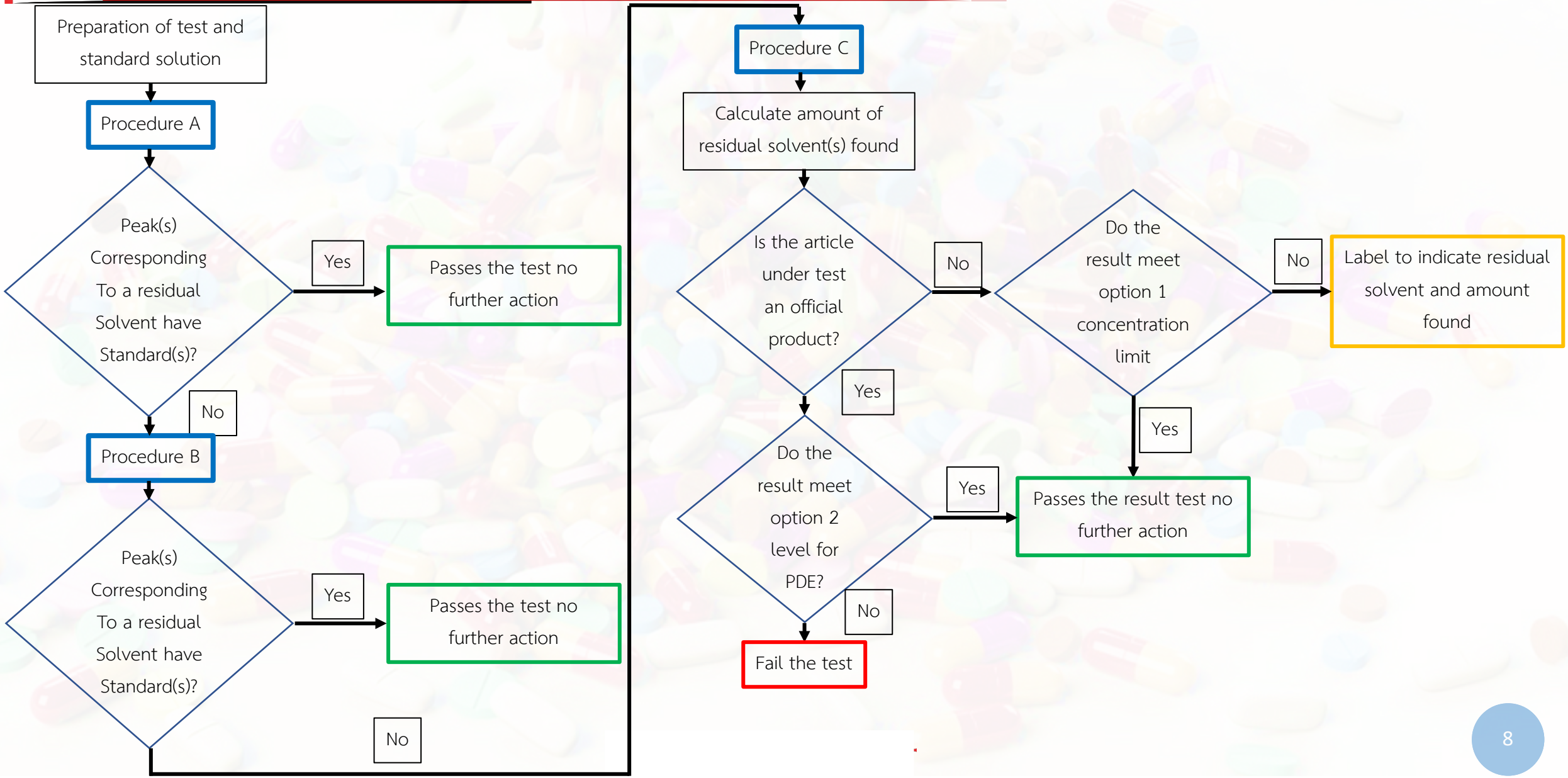


Identification, Control and Quantification

Class 1 and Class 2 Residual Solvents Procedure

- **Procedure A**, Screens for and confirms the solvents' presence using a G43 (volatiles) column.
- **Procedure B**, Confirms the solvents' identity using a G16 (wax) column.
- **Procedure C**, Which also uses a G43 column, is required to quantify the amount of residual solvents present.

Diagram relating to the identification limit tests.



Procedure A: Requirements

GC Parameter	
Column	G43 (Thermo Scientific™ TraceGOLD™ TG 624) 30 m × 0.32 mm × 1.8 µm (P/N 26085-3390) 30 m × 0.53 mm × 3.0 µm (P/N26085-3960)
Split ratio	1:5
Oven Temp.	40 °C hold 20 min. ramp to 240 °C with 10 °C/min. hold 20 min.
Injector Temp.	140
FID Temp.	250

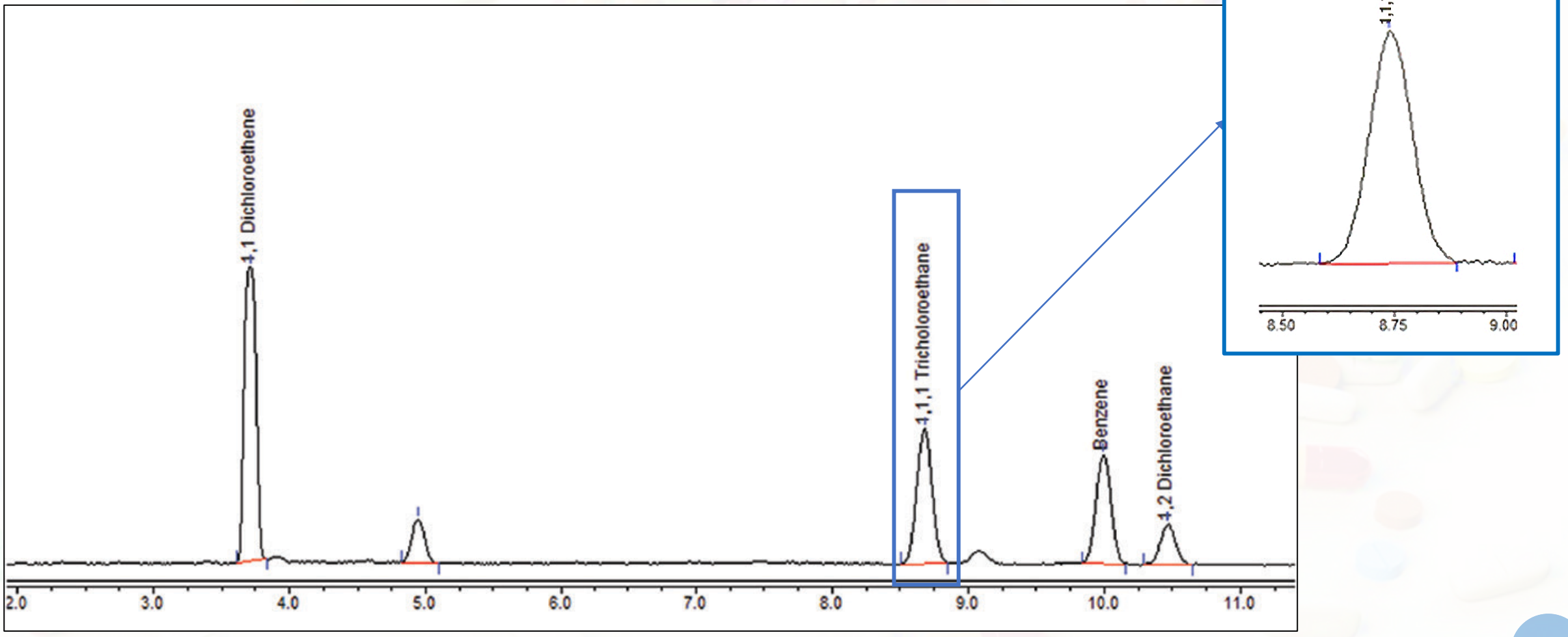
Headspace Operating Parameter Sets			
	1	2	3
Equilibration Temp. (°C)	80	105	80
Equilibration Time (min)	60	45	45
Transfer-line Temp. (°C)	85	110	105
Carrier gas: nitrogen or helium at an appropriate pressure			
Pressureization time (s)	30	30	30
Injection volume (mL)	1	1	1

Procedure A: System Suitability

- **Class 1 Standard Solution**
  - Signal-to-noise ratio of 1,1,1-trichloroethane is not less than 5
- **Class 1 System Suitability Solution**
  - Signal-to- noise ratio of each peak is not less than 3
- **Class 2 Mixture A Standard Solution**
  - Resolution (R) between acetonitrile and methylene chloride (Dichloromethane) is not less than 1.0

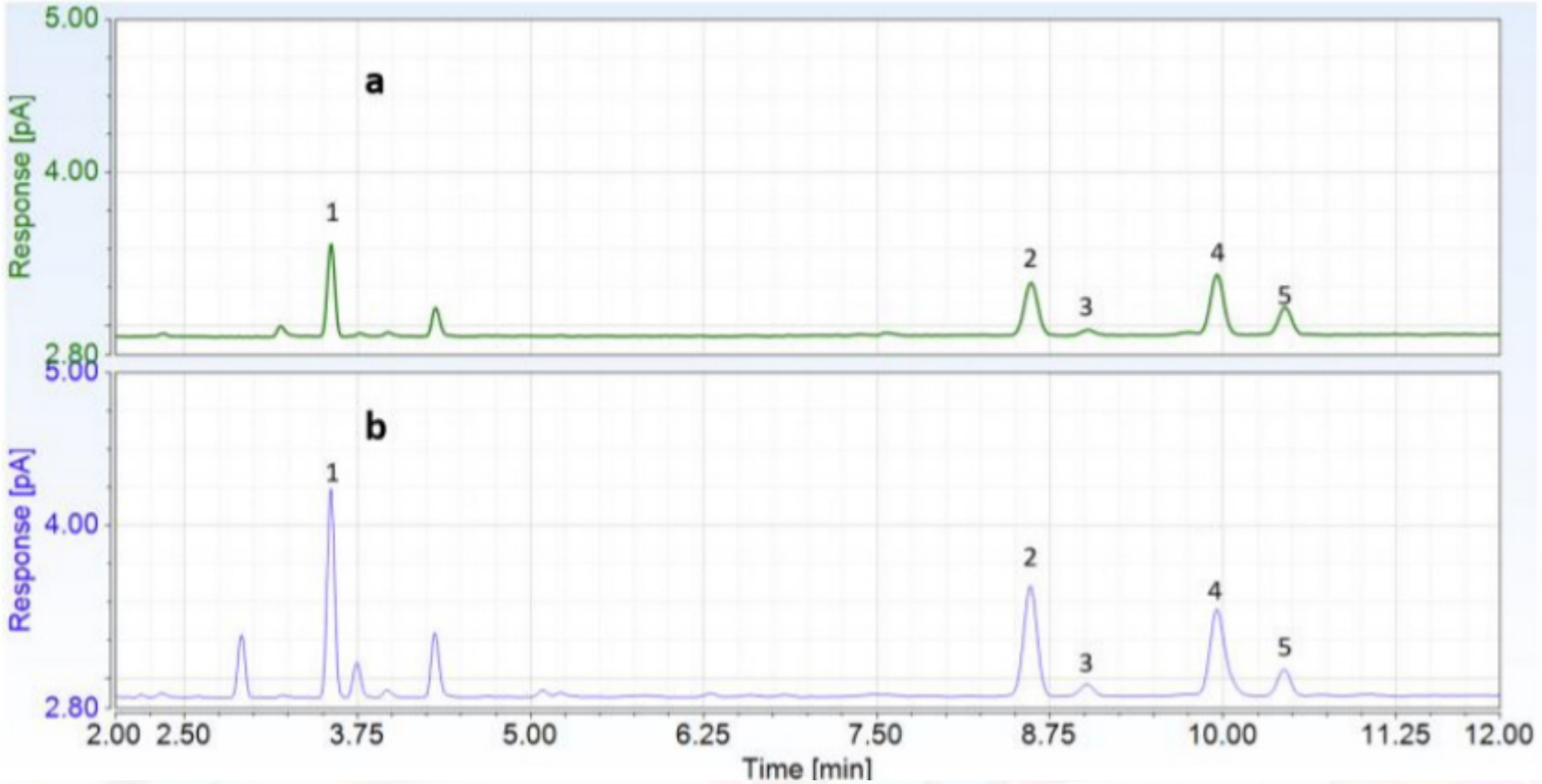
Procedure A: System Suitability result

Class 1 Standard Solution



Procedure A: System Suitability result

Class 1 System Suitability Solution



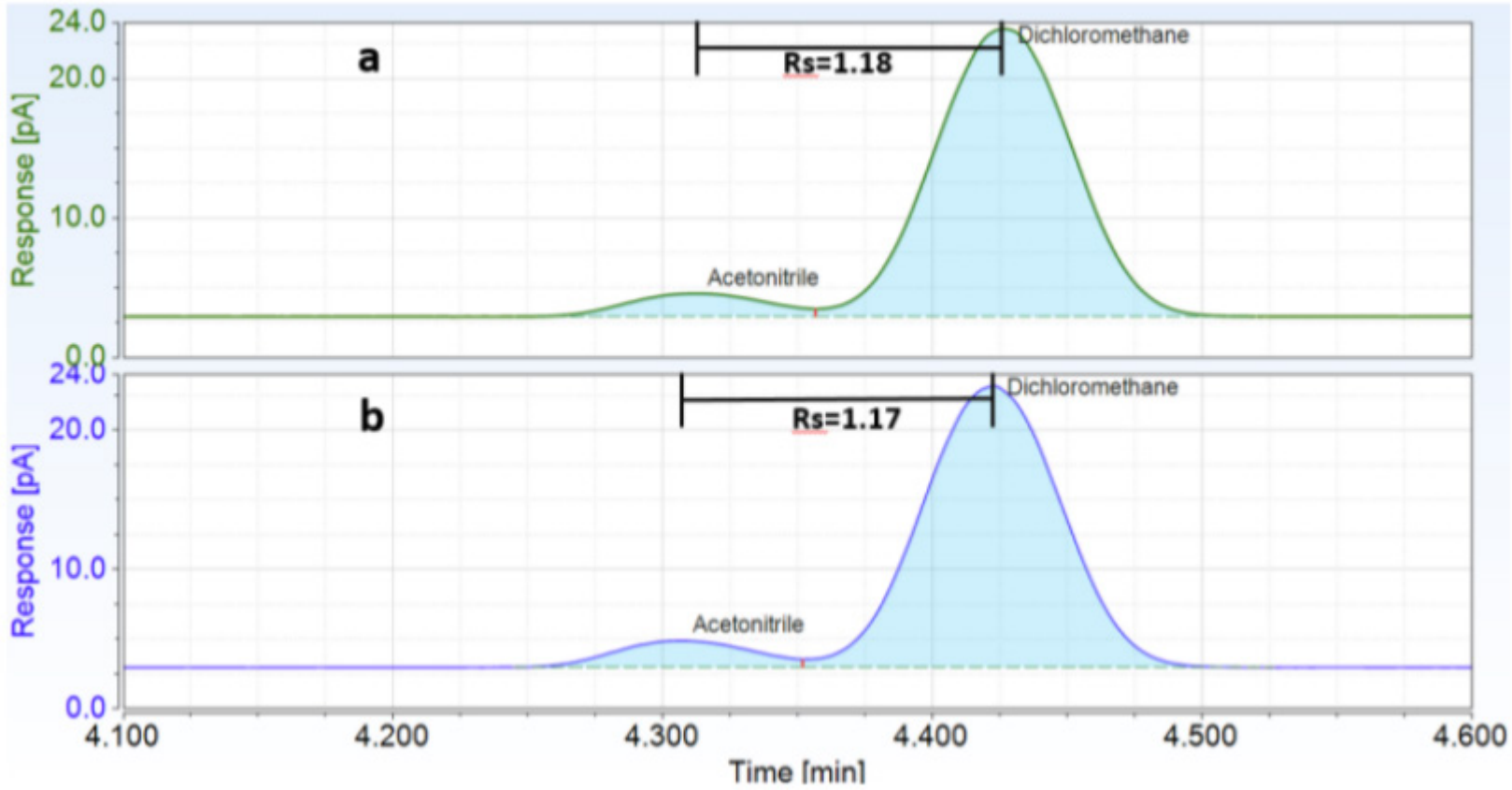
1 = 1,1-Dichloroethene **S/N 126**
2 = 1,1,1-Trichloroethane **S/N 82**
3 = Carbon Tetrachloride **S/N 8**
4 = Benzene **S/N 98**
5 = 1,2-Dichloroethane **S/N 41**

1 = 1,1-Dichloroethene **S/N 769**
2 = 1,1,1-Trichloroethane **S/N 104**
3 = Carbon Tetrachloride **S/N 11**
4 = Benzene **S/N 79**
5 = 1,2-Dichloroethane **S/N 25**

Class 1 system suitability solution peak-to-peak signal-to-noise (S/N) ratios for water-soluble (a) and water insoluble (b) products.

Procedure A: System Suitability result

Class 2 Mixture A Standard Solution



Chromatographic resolution (Rs) between acetonitrile and dichloromethane for water-soluble (a) and water-insoluble products (b).

Procedure B : Requirements

GC Parameter	
Column	G16 (Thermo Scientific™ TraceGOLD™ TG WaxMS) 30 m × 0.32 mm × 0.25 µm (P/N 26088-1430) 30 m × 0.53 mm × 0.25 µm (P/N 26088-1440)
Split ratio	1:5
Oven Temp.	50 °C hold 20 min. ramp to 165 °C with 6 °C/min. hold 20 min.
Injector Temp.	140
FID Temp.	250

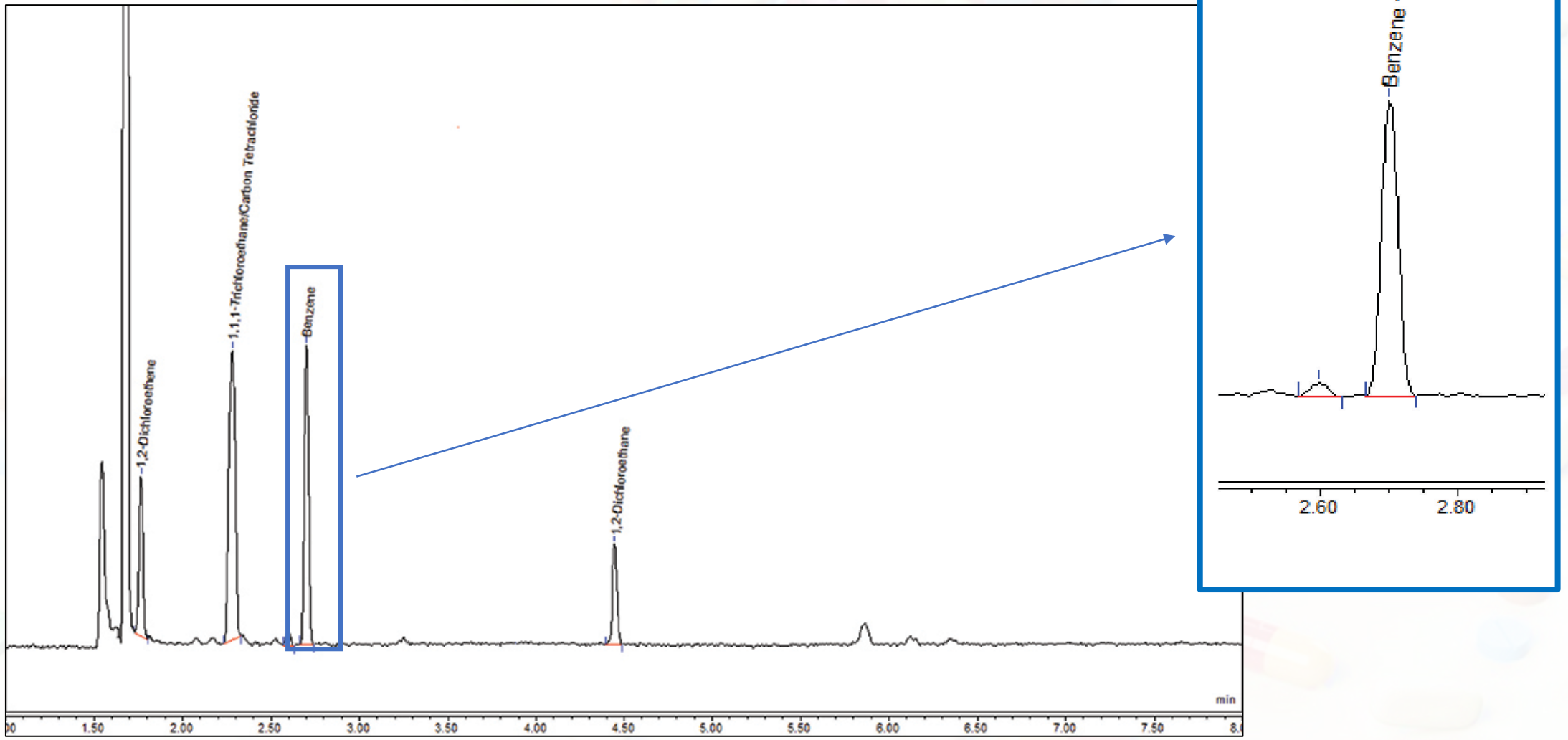
Headspace Operating Parameter Sets	1	2	3
Equilibration Temp. (°C)	80	105	80
Equilibration Time (min)	60	45	45
Transfer-line Temp. (°C)	85	110	105
Carrier gas: nitrogen or helium at an appropriate pressure			
Pressureization time (s)	30	30	30
Injection volume (mL)	1	1	1

Procedure B : System Suitability

- Class 1 Standard Solution
  - Signal-to-noise ratio of benzene is not less than 5
- Class 1 System Suitability Solution
  - Signal-to-noise ratio of each peak in the is not less than 3
- Class 2 System Suitability Solution
  - Resolution (R) between acetonitrile and trichloroethylene is not less than 1.0

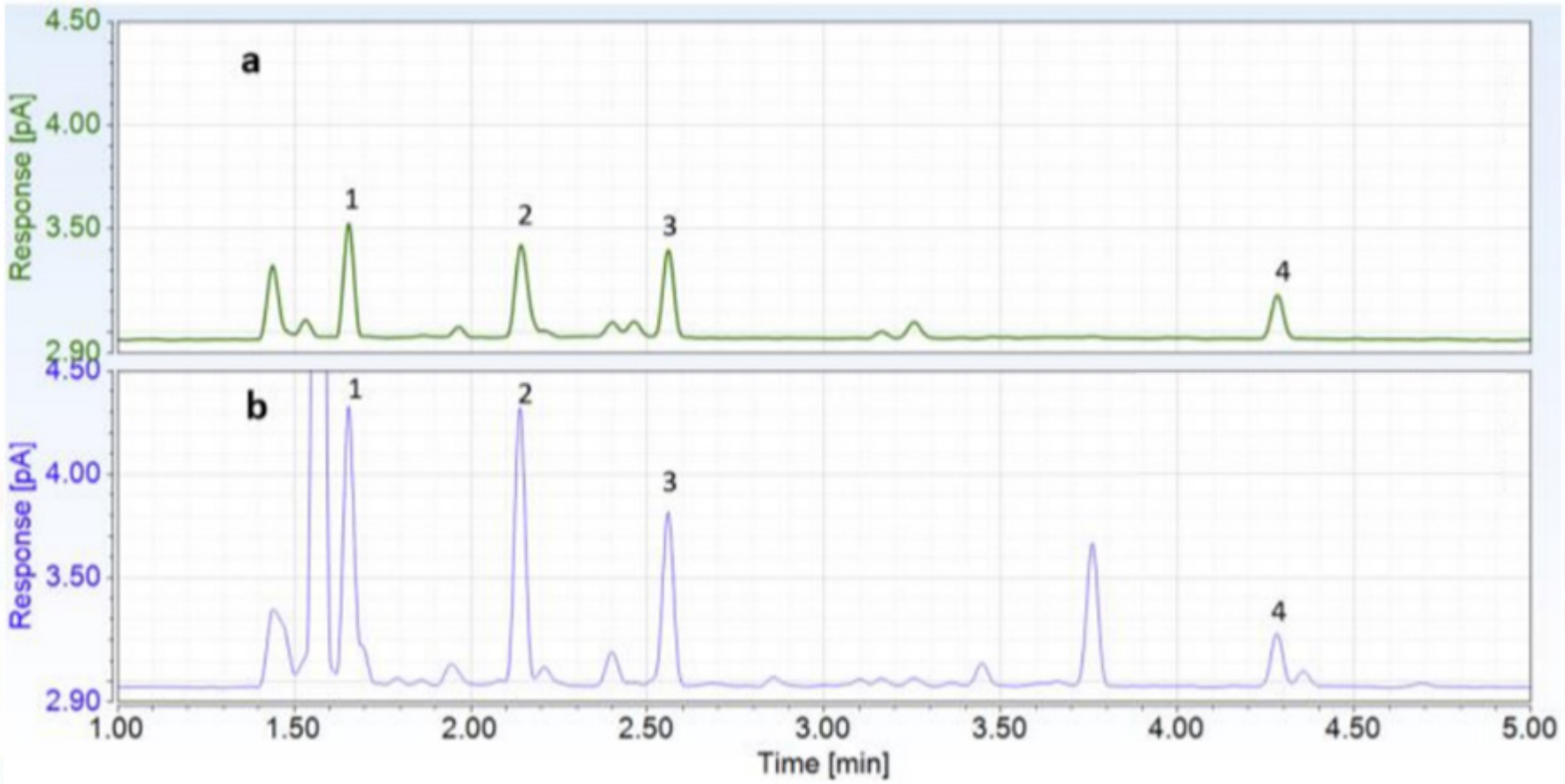
Procedure B: System Suitability result

Class 1 Standard Solution



Procedure B: System Suitability result

Class 1 System Suitability Solution



1 = 1,1-Dichloroethene **S/N 114**

2 = 1,1,1-Trichloroethane **S/N 376**

3 = Benzene **S/N 25**

4 = 1,2-Dichloroethane **S/N 40**

1 = 1,1-Dichloroethene **S/N 75**

2 = 1,1,1-Trichloroethane **S/N 214**

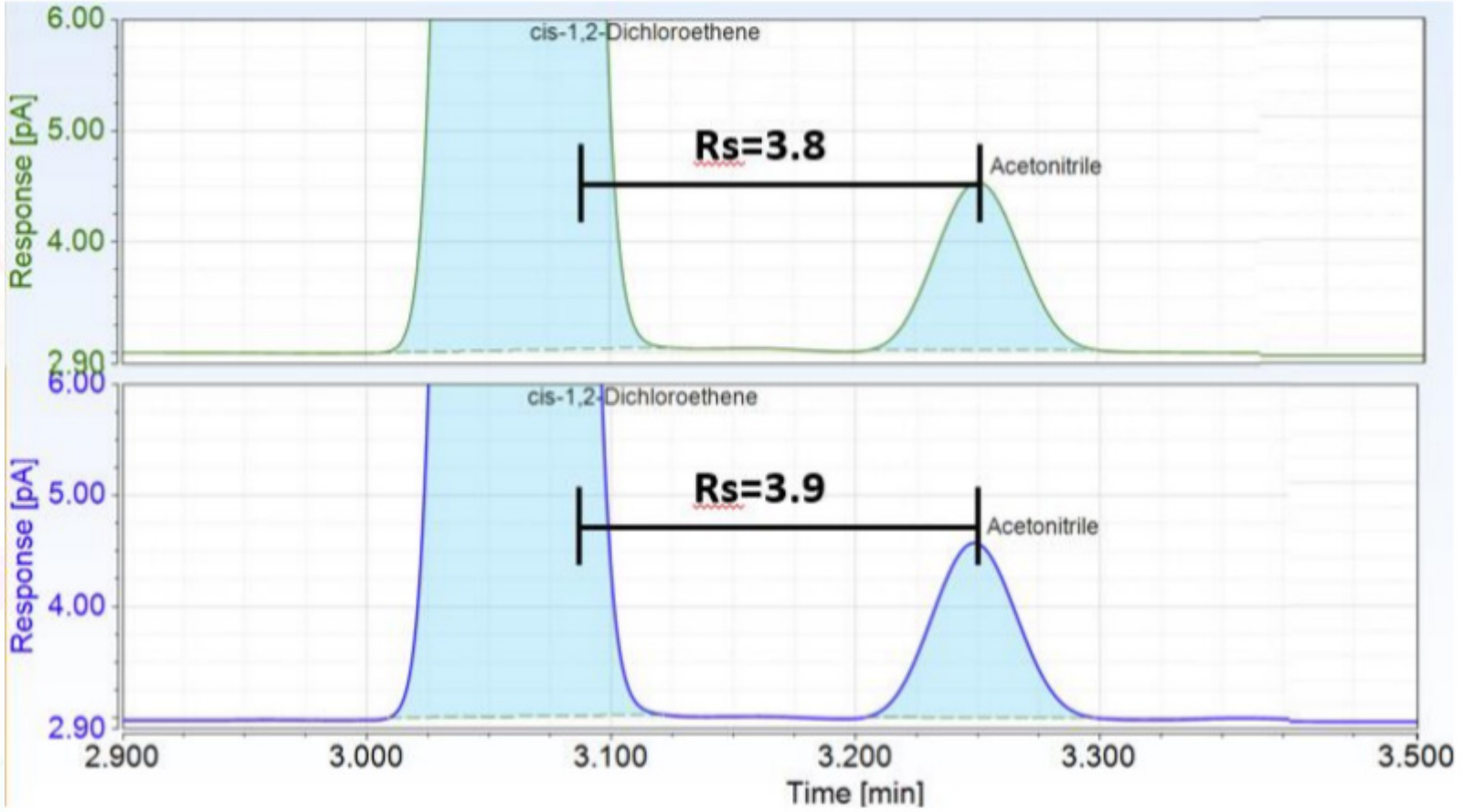
3 = Benzene **S/N 112**

4 = 1,2-Dichloroethane **S/N 23**

Peak-to-peak signal-to-noise (S/N) ratios for Class 1 system suitability solutions for water-soluble (a) and water-insoluble (b) products.

Procedure B: System Suitability result

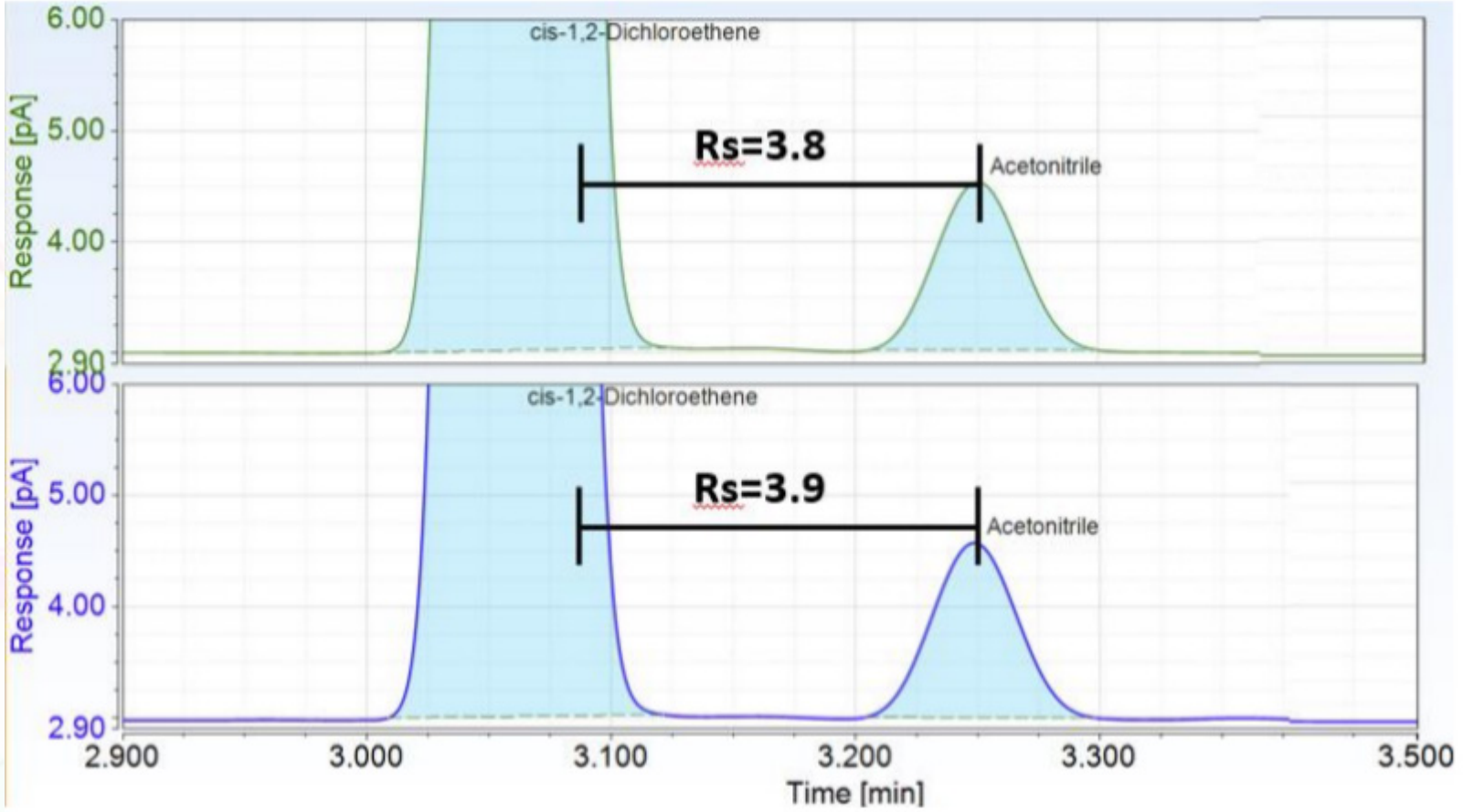
Class 2 System Suitability Solution



Chromatographic resolution (Rs) between cis 1,2-dichloroethene and acetonitrile for watersoluble (a) and water-insoluble products (b).

Procedure B: System Suitability result

Class 2 System Suitability Solution



Chromatographic resolution (Rs) between cis 1,2-dichloroethene and acetonitrile for watersoluble (a) and water-insoluble products (b).

Procedure C Requirements:

Perform the analysis following the instructions for **Procedure A** with the same instrument configuration on the standard solution, the test solution, and the spiked test solution.

Calculate the amount in ppm for each residual solvent found using the formula:

1. $\text{Result} = 5(C/W)[r_u / (r_{st}-r_u)]$ ..... QUANTIFICATION FOR WATER-SOLUBLE

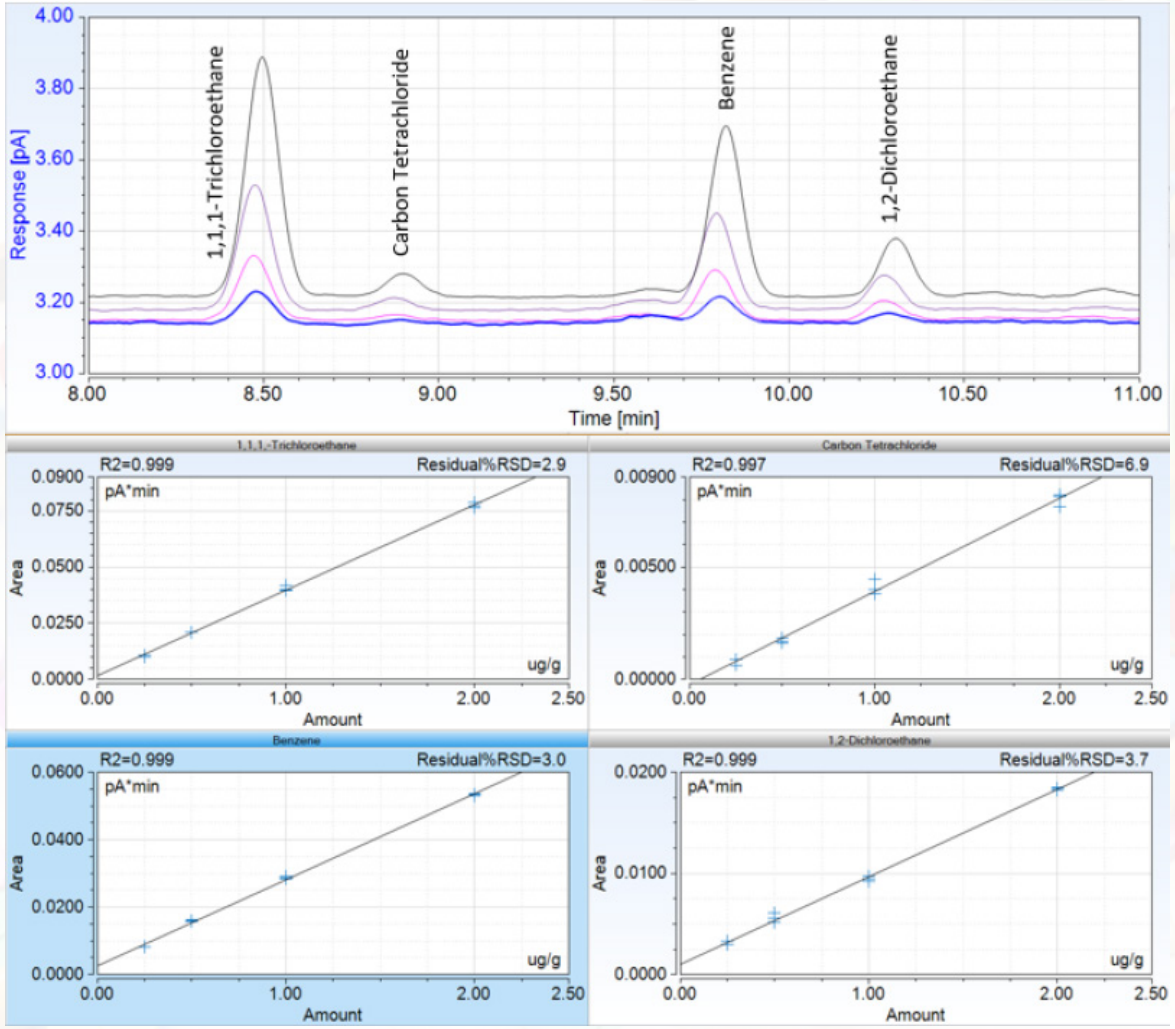
2. $\text{Result} = 10(C/W)[r_u / (r_{st}-r_u)]$..... QUANTIFICATION FOR WATER-INSOLUBLE

C is the concentration in µg per mL of the reference standard in the standard stock solution;

W is the weight in grams of the article under test used to prepare the test stock solution;

r_u and r_{st} are the peak responses of each residual solvent obtained from the test solution and the spiked test solution, respectively.

Linearity



Calibration curves

(at 1 2 5 25 50 and 100 of the concentration limit)

for some of the Class 1 residual solvents

Performance

Compound name	%RSD (n=18)		Correlation coefficient (R^2)	Residuals standard deviation (%RSD)
	Water	DMSO		
1,1-Dichloroethene	1.5	0.7	1.000	2.0
1,1,1-Trichloroethane	1.0	0.8	0.999	2.9
Carbon Tetrachloride	4.9	2.9	0.997	6.9
Benzene	0.8	0.9	0.999	3.0
1,2-Dichloroethane	1.6	1.0	0.999	3.7
Methanol	0.7	1.4	1.000	1.4
Acetonitrile	0.8	1.6	1.000	1.7
Dichloromethane	3.1	0.7	0.998	4.2
trans 1,2-Dichloroethene	4.0	1.2	0.999	2.9
cis 1,2-Dichloroethene	3.4	0.8	0.998	5.0
Tetrahydrofuran	0.9	1.4	1.000	2.2
Cyclohexane	3.6	2.8	0.999	3.0
Methylcyclohexane	3.0	2.4	1.000	2.5

Compound name	%RSD (n=18)		Correlation coefficient (R^2)	Residuals standard deviation (%RSD)
	Water	DMSO		
1,4-Dioxane	1.3	1.9	1.000	1.5
Toluene	3.6	0.8	0.997	5.6
Chlorobenzene	3.3	0.7	0.999	2.8
Ethylbenzene	3.4	0.9	0.997	5.3
m-Xylene	3.3	0.9	0.996	6.0
p-Xylene	3.3	0.9	0.996	6.0
o-Xylene	3.1	0.8	0.997	5.6
Hexane	1.2	0.8	0.998	5.8
Nitromethane	2.9	1.5	0.998	4.8
Chloroform	0.9	1.0	0.999	3.0
1,2-Dimethoxyethane	1.4	0.9	0.997	8.4
Trichloroethene	1.9	0.7	0.999	2.9
2-Hexanone	0.6	0.4	1.000	1.3
Tetralin	0.9	0.6	0.999	3.0

Peak area RSDs obtained from n= 18 consecutive injections using water and DMSO as diluents for the concentrated standard solutions, correlation coefficients (R 2 and relative standard deviation of residuals RSD) obtained over four calibration levels at 1 2 5 25 50 and 100 of the concentration limits

Conclusions

- All the USP <467> method acceptance criteria were met, and the chromatograms show good peak shapes and resolution.

- These data demonstrate that headspace-gas chromatography is a quantitative technique that easily meets the requirements of the USP <467> method.

- The system configuration of the TRACE 1310 GC, TriPlus 500 Headspace, and Chromeleon CDS is a solid, fully integrated, and reliable platform to perform the analysis according to the USP <467> method with full auditing capability. Operating this system configuration and method in a regulated environment is highly possible obtaining accurate, dependable results.

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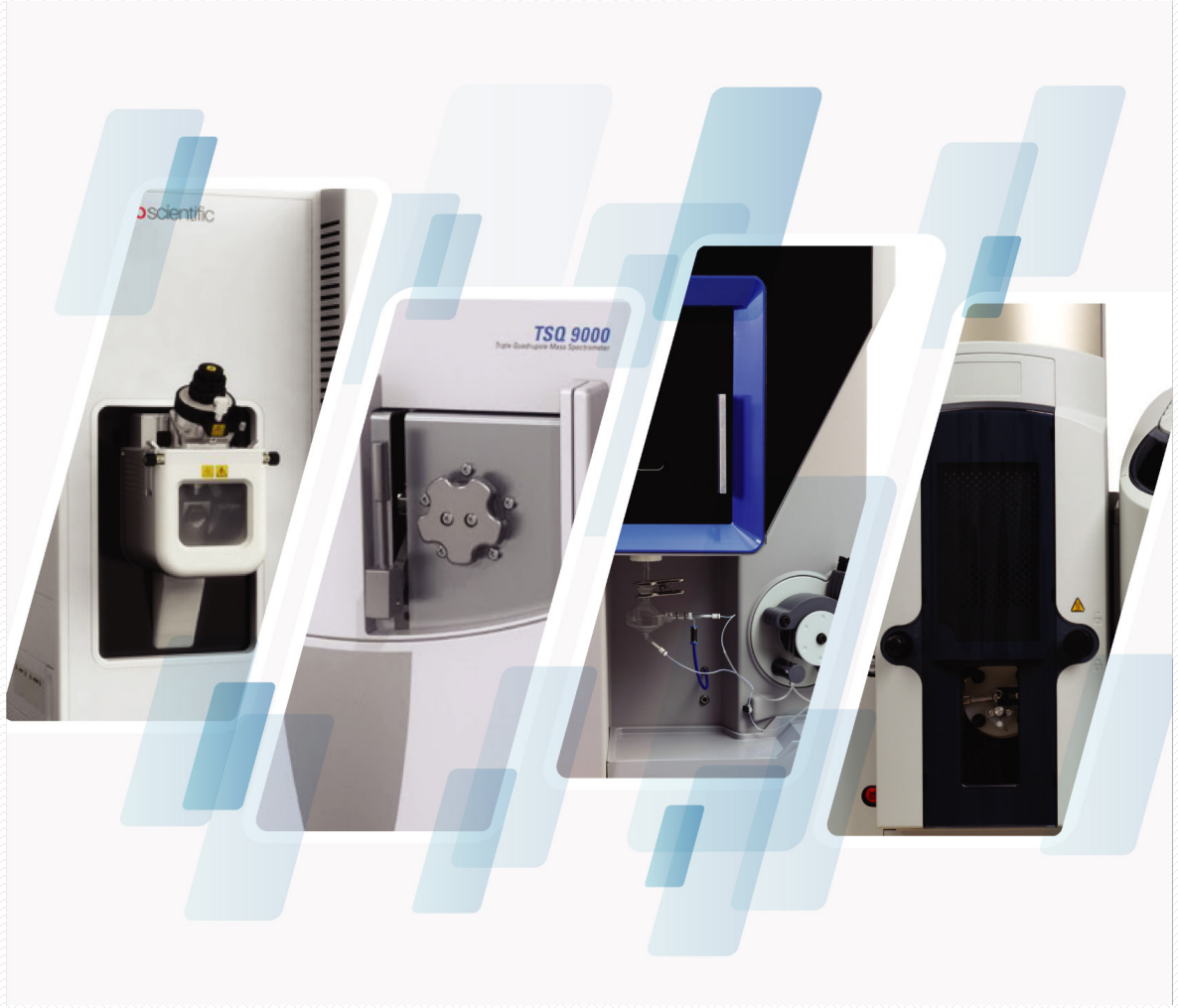

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