The Analysis of Residual Solvents in Pharmaceuticals using Headspace GC

White Paper

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Abstract

Pharmaceutical products come in to contact with residual solvents throughout their manufacturing and production processes. They are classified depending on their risk to human health and therefore the analysis of residual solvents is an important pharmacopeia testing requirement that regulatory organisations, for example the US Food and Drug administration (FDA) and the Medicines and Healthcare Products Regulatory Agency (MHRA), regard as highly important.

The following white paper will provide an overview of residual solvent testing as per the United States (US) Pharmacopeia and the testing carried out at Reading Scientific Services Ltd (RSSL).

Introduction

Residual solvents are organic volatile impurities that can occur in the manufacture of Active Pharmaceutical Ingredients (APIs). Residual solvents can also be present in the production of raw materials required for the production of pharmaceutical drug products.

Residual solvents are classified as Class 1, 2 or 3 dependent on their exposure limits and risk to human health. Class 3 residual solvents pose the lowest risk to human health and Class 1 solvents pose the highest risk based on toxicity. Due to this, Class 1 solvents are therefore not to be used or present during pharmaceutical manufacture, unless their use can be strongly justified due to a significant therapeutic advantage.

Class 2 residual solvents have a concentration limit in parts per million which is related to the controlled daily exposure limit (mg/day). Both Class 1 and 2 residual solvents hold carcinogenic, toxicological and environmental concerns.

US Pharmacopeia Requirements

The USP general chapter <467> has been in effect since 2008 for residual solvent analysis and describes residual solvent screening, identification and quantification following three procedures, by headspace GC-FID (HS-GC). These procedures are able to identify and quantify Class 1, 2A and 2B residual solvents in drug products. Class 3 solvents are also able to be quantified when the specific solvent is requested.

See Table 1, 2 and 3 for full listing of residual solvents that are able to be quantified.

Solvent	Concentration limit (ppm)	Exposure Risk
1,1-Dichloroethene	8	Toxic
1,1,1-Trichloroethane	1500	Environmental Hazard
Carbon Tetrachloride	4	Toxic and Environmental Hazard
Benzene	2	Carcinogenic
1,2,-Dichloroethane	5	Toxic

Table 1: Class 1 Residual Solvents (solvents that should be avoided)

Solvent	Concentration limit (ppm)	Permitted Daily Exposure (mg/day)
Acetonitrile	410	4.1
Chlorobenzene	360	3.6
Cumene	70	0.7
Cyclohexane	3880	38.8
1,2-Dichloroethene	1870	18.7
Methylene Chloride	600	6.0
1,4-Dioxane	380	3.8
Methanol	3000	30.0
Methylcyclohexane	1180	11.8
Tetrahydrofuran	720	7.2
Toluene	890	8.9
Xylenes	2170	21.7

Table 2: Class 2A Residual Solvents

Solvent	Concentration limit (ppm)	Permitted Daily Exposure (mg/day)
Chloroform	60	0.6
1,2-Dimethoxyethane	100	1.0
Hexane	290	2.9
Methylbutylketone	50	0.5
Nitromethane	50	0.5
Pyridine	200	2.0
Tetralin	100	1.0
Trichloroethylene	80	0.8

Table 3: Class 2B Residual Solvents

USP <467> method procedures

The USP chapter consists of three methods of analysis; Procedure A is a screening approach for all Class 1, 2A and 2B solvents. Procedure B is a confirmatory stage and is used if Procedure A cannot truly verify the residual solvents present. Both procedures are followed to identify and semi-quantify residual solvents when they are likely but not definitively known to be present in the raw material or active ingredient. When the residual solvent that is present in a sample is known and this information is available, then Procedure C is followed to successfully quantify the amount of residual solvent present and whether this passes the concentration limits.

See the flow diagram to the right (Figure 1) for the steps taken as part of the residual solvents limit test.

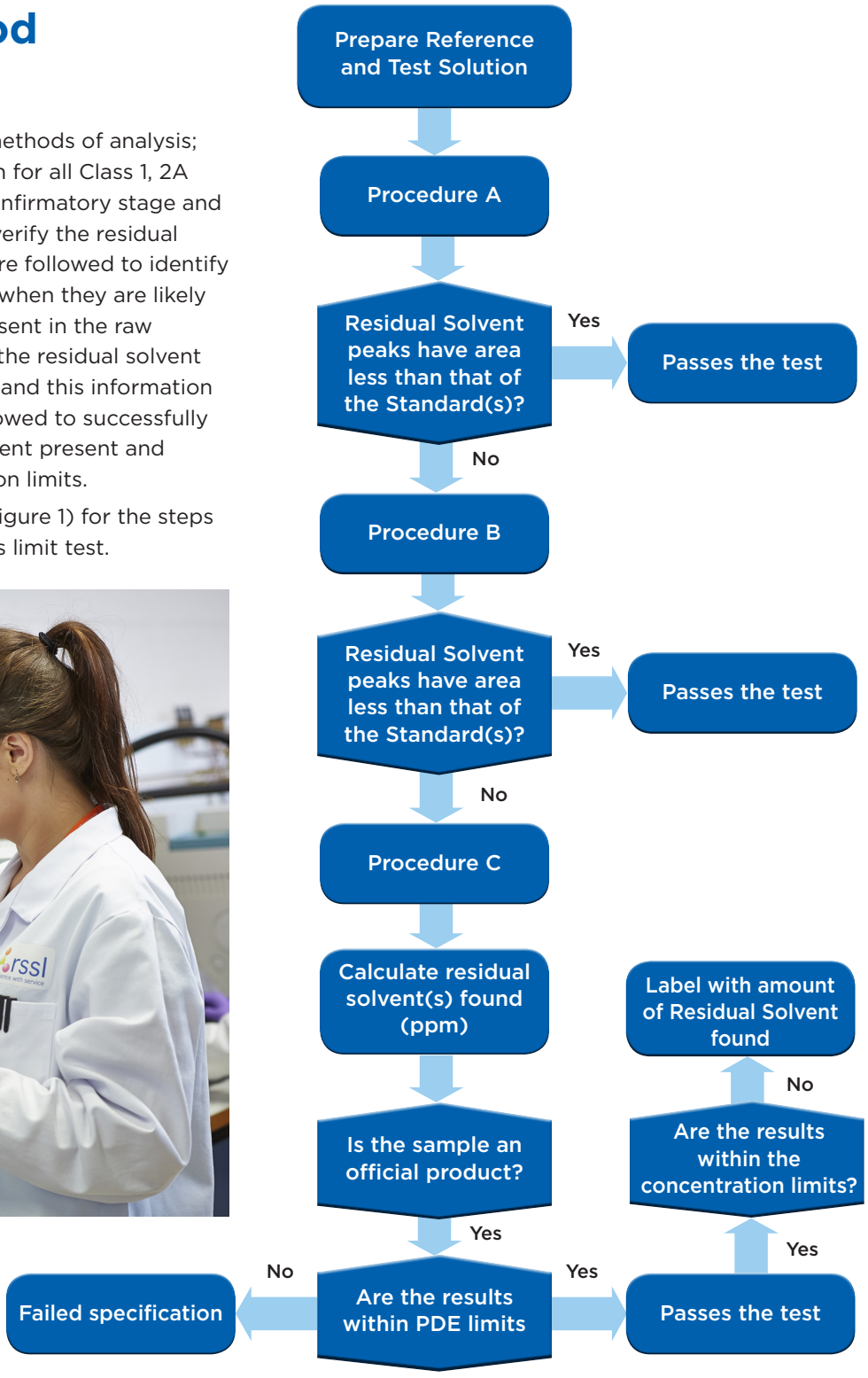

Figure 1: Residual Solvent Flow Diagram of experimental steps

Residual Solvent Case Study at RSSL

Shortcomings in the USP Method

Many QC laboratories encounter issues when trying to comply to USP general chapter <467>. This is due in part to the concentrations of Class 1 solvents and due to the sensitivity required to conform to system suitability requirements, especially relating to the Signal to Noise ratio for Carbon Tetrachloride.

RSSL has partnered with Perkin Elmer to overcome these shortcomings and is therefore able to offer this analysis to clients.

Methodology at RSSL

Residual Solvent, Procedure A for water-insoluble articles, is performed using a Clarus 680 GC with FID detection and a Turbomatrix HS-110 sampler.

Conditions are outlined in tables 4 and 5 below.

These two systems have been selected for their high sensitivity and we have a large number of these instruments here at RSSL.

GC Conditions	
Oven:	40°C for 20 minutes, 10°C/min to 240°C, hold for 20 minutes.
Injector:	140°C, Split ratio 3:1*
Carrier:	35 cm/sec (Helium)
Detector:	250°C (FID)
Detection Gases:	H_2: 45 ml/min
	Air: 450 ml/min
Analytical Column:	VF-624ms, G43, 30m x 0.53mm x 3.0µm

Table 4: Chromatographic Conditions

*During this analysis the split ratio was adjusted to optimise sensitivity, this is allowed as stated in the USP General Chapter <467>.

Headspace conditions	
Pressure Regulator:	20 psi (He)
Equilibrium Conditions:	80°C for 45 minutes
Needle Temperature:	90°C
Transfer Line Temperature:	105°C
Pressuring Time:	2.0 minutes
Injection Volume:	1.0 ml
GC Cycle Time:	75 minutes

Table 5: Headspace Conditions

We routinely use Perkin Elmer GC systems with their higher sensitivity and increased efficiency between runs. This allows the identification, confirmation and quantification of Residual Solvents from Class 1, Class 2A, Class 2B and Class 3 to be analysed effectively and we are able to offer this service to our clients.

The solvents conducted in this investigation were analysed following the water insoluble methodology, but the same results can be expected with water soluble samples. The choice of diluent is chosen dependent on the solubility of the sample under test and the residual solvent response is dependent on the diluent used.

Class 1, 2A and 2B solutions were prepared to the concentration limits as specified in the USP. All system suitability criteria passed as per the USP requirements:

'The signal-to-noise ratio of 1,1,1-trichloroethane in the Class 1 Standard Solution is NLT 5; the signal-to-noise ratio of each peak in the Class 1 System Suitability Standard Solution is NLT 3; and the resolution, R, between acetonitrile and methylene chloride in the Class 2 Mixture A Standard Solution is NLT 1.0'.

The S/N ratio of Carbon Tetrachloride (which is the smallest peak present) in the Class 1 Standard gave a value of 7.1 therefore conforming against the system suitability specification limit.

See Figure 2 for an example of a Class 1 Standard Solution run on a Perkin Elmer GC system. Figure 3 and Figure 4 also highlight Class 2A Standard Stock Solution and Class 2B Standard Stock Solution respectively.

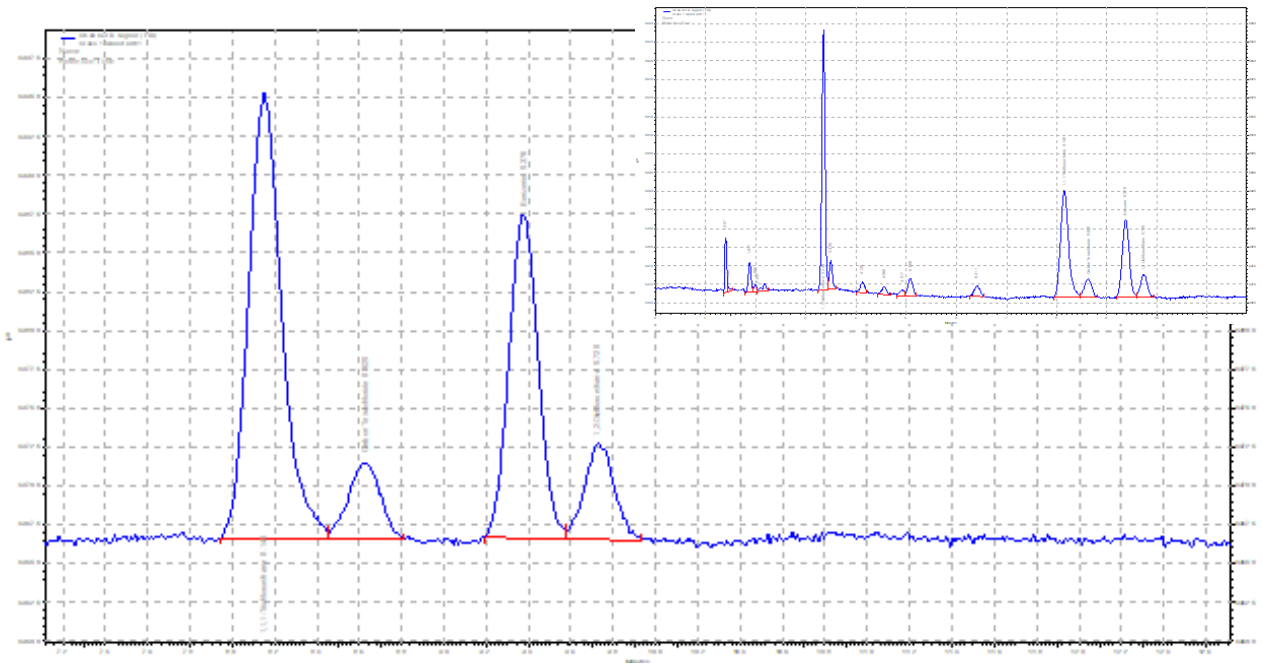

Figure 2: Carbon Tetrachloride peak on Class 1 Standard

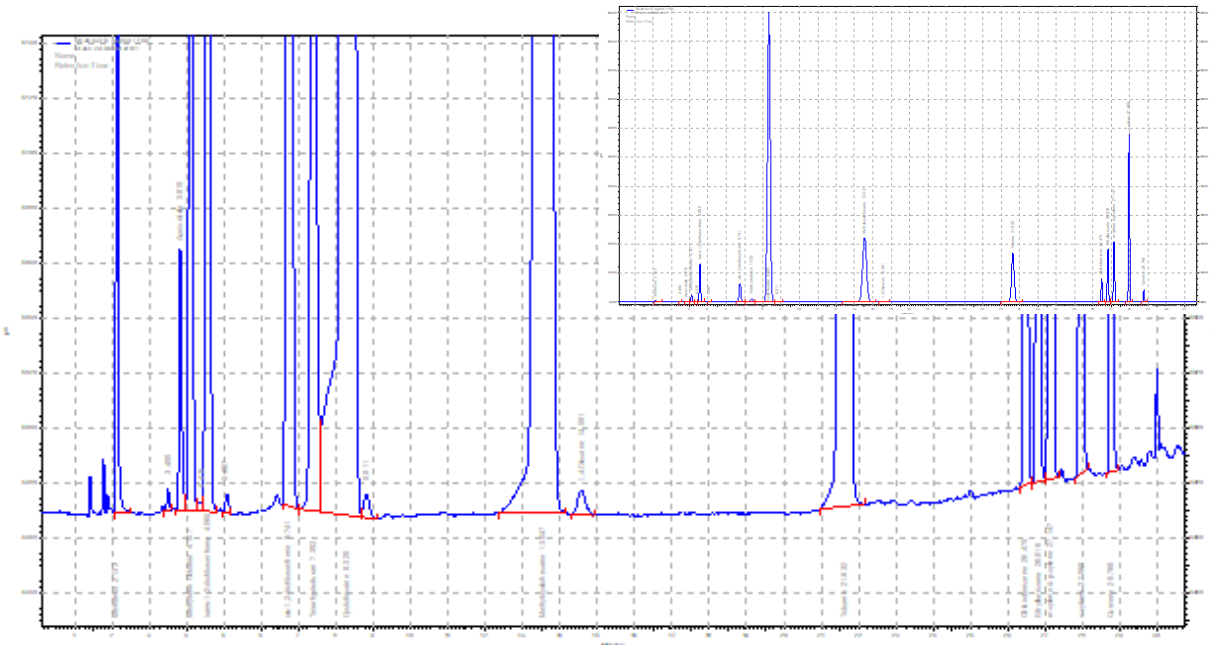

Figure 3: Class 2A Standard Stock Solution

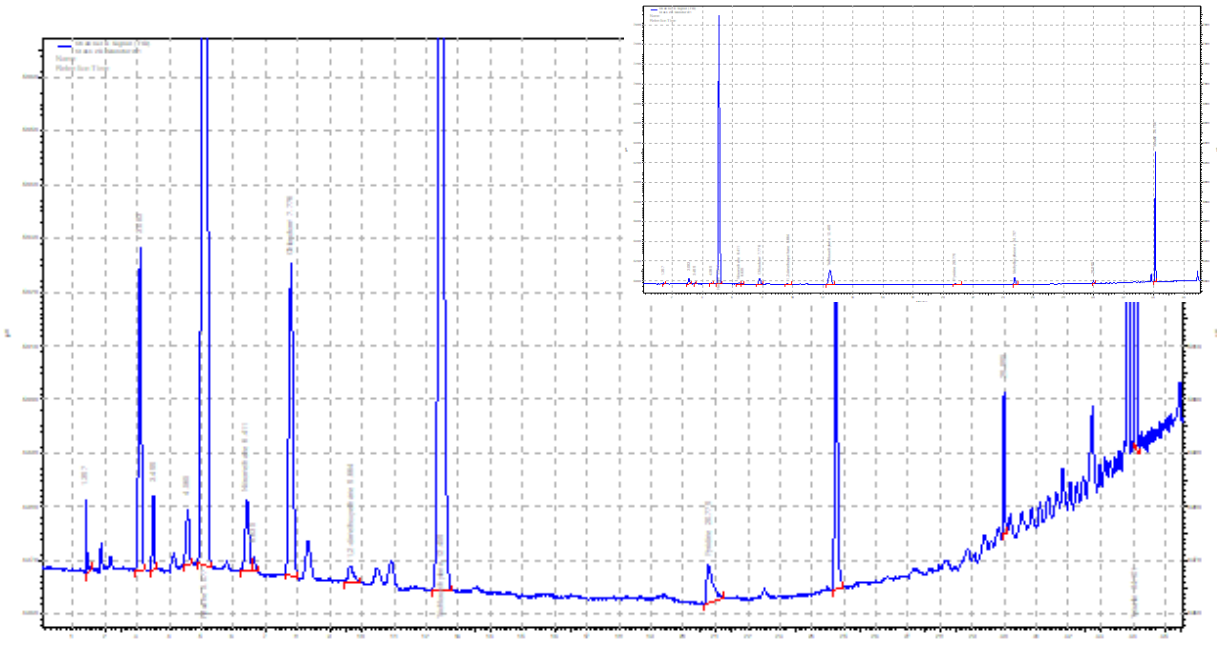

Figure 4: Class 2B Standard Stock Solution

Conclusion

The Perkin Elmer GC system highlights high sensitivity and these systems are therefore able to successfully reach the sensitivity levels required for the analysis of residual solvents. We have a number of Perkin Elmer systems and therefore using this instrumentation along with our laboratory expertise we are able to routinely carry out Residual Solvent screening and targeted residual solvent analysis. Our laboratory expertise means that at RSSL, we have an understanding of the residual solvents under test, the drug product and also expertise with our extensive range of GC systems and detectors available. We routinely carry out Procedure A, Procedure B and Procedure C residual solvent analysis, along with a wide variety of pharmacopeia and investigative testing.

RSSL is an industry leading laboratory providing GMP quality control analysis of raw materials, APIs, excipients and drug products to comply with appropriate standards, according to pharmacopoeia monographs and client methods. Our full suite of equipment means we can offer chemical and physical analysis for more than 95% of pharmacopoeial monographs. To find out more about our GMP quality control services, please contact us on: +44 (0)118 918 4076, email enquiries@rssl.com, or visit www.rssl.com

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Kate joined RSSL upon graduating from University with a first class honours in Chemistry with Industrial experience. Kate has worked in the CRO industry mainly focusing on Pharmaceutical Chemistry specialising in wet chemistry, Gas Chromatography, Gas Chromatography Mass Spectrometry and project management.

About Reading Scientific Services Ltd (RSSL)

RSSL is firmly established as a trusted partner in the provision of analytical, investigational, consultancy and training services to clients in the food, consumer goods, pharmaceutical, biopharmaceutical and healthcare sectors.

Our chemical, physical, biochemical, biological and microbiological services are wide ranging, and provide support through the full product lifecycle. RSSL is routinely inspected by the MHRA, FDA and UKAS which ensures that our analytical services meet the needs of industry. We are trusted by industry to provide a solution with scientific excellence, outstanding customer service and professionalism.

Contact us to find out more about our expertise and how we can support you:

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