A proficiency testing scheme for the analysis of residual solvents in pharmaceutical products

LGC

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Introduction

Residual solvents in pharmaceuticals may be generally defined as organic volatile chemicals that are used or produced in the manufacture of drug substances or excipients, or in the preparation of drug products. Since there is no therapeutic benefit from residual solvents, all residual solvents should be removed to the extent possible to meet product specifications, good manufacturing practices, or other quality based requirements.
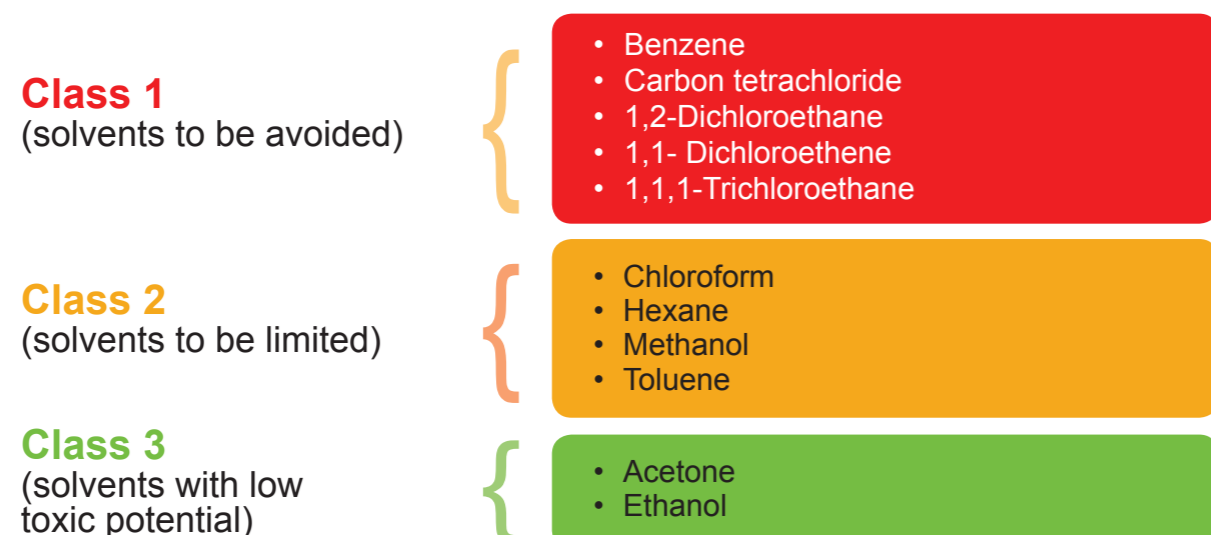
Test material

A proficiency testing sample, for the quantification of residual solvents has been developed and introduced into the LGC PHARMASSURE scheme. The sample 2E - Residual solvents was provided on two occasions in the 2016/2017 scheme year, to customers in a number of countries worldwide.

The initial format of the sample was based on a 'matrix' and a spike solution.

**Picture 1:** Format of sample 2E - Residual solvents.

PHARMASSURE

Instruction sheet

2E - Residual solvents

Figure 1: A list of parameters present in sample 2E - Residual solvents.

Class 1
(solvents to be avoided)

- Benzene
- Carbon tetrachloride
- 1,2-Dichloroethane
- 1,1- Dichloroethene
- 1,1,1-Trichloroethane

Class 2
(solvents to be limited)

- Chloroform
- Hexane
- Methanol
- Toluene

Class 3
(solvents with low toxic potential)

- Acetone
- Ethanol

Methodology

Figure 3: Pharmacopoeia procedures and analytical methods for the quantification of residual solvents.

Ph. Eur. 2.4.24

USP 467

Ph. Eur. 2.2.28

GC-MS

GC-FID

Loss on Drying
Class 3 only
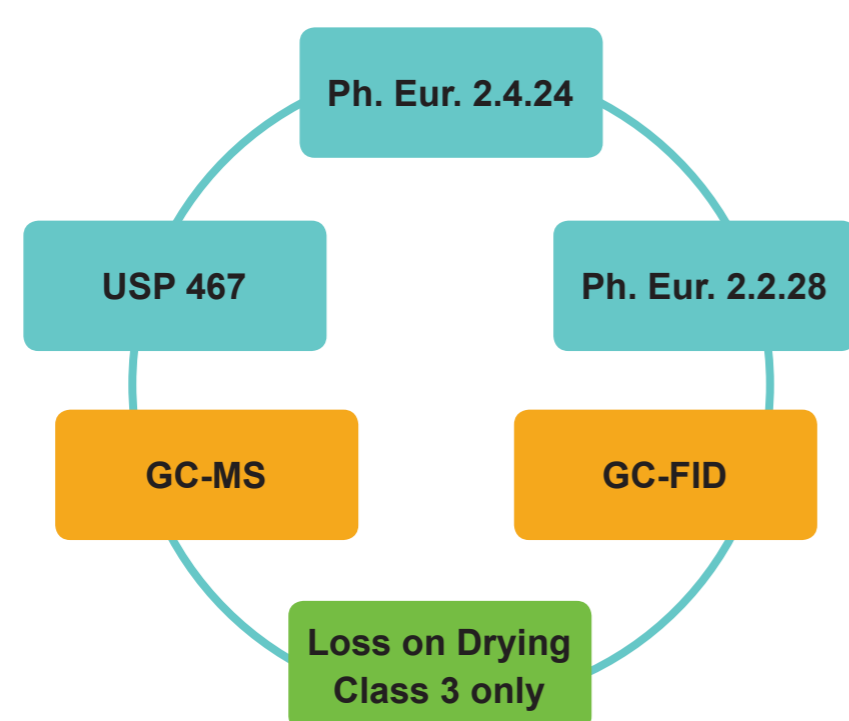
Statistical evaluation

The assessment of participants was carried out using the robust mean (median) of the participant results to calculate the Assigned Value (AV) and the robust standard deviation of the participant results as the Standard Deviation for Proficiency Assessment (SDPA).

Figure 4: Statistical evaluation of Ethanol in PHARMASSURE round 60.

Sample: 2E - Residual Solvents#
Analyte: Ethanol#

Lab ID	Method	Result (µg/g)	Ux (µg/g)	z' score*
PH0045	GC-MS	3,554		1.30
PH0060	GC-FID	2,782		0.14
PH0077	Ph. Eur. 2.2.28	2,854	407	0.25
PH0156	Ph. Eur. 2.2.28	38		-3.97
PH0279	Ph. Eur. 2.2.28	2,984	112	0.44
PH0479	GC-FID	34		-3.97
PH0496	Ph. Eur. 2.4.24	2,593	500	-0.14
PH0497	GC-MS	2,160	59	-0.79

Data Statistics

	Value
Number of Results	8
Number of Excluded Results	0
Mean	2,125 µg/g
Median	2,688 µg/g
Standard Deviation	1,346.5 µg/g
Robust Standard Deviation	611.0 µg/g
Result Range	34 to 3,554 µg/g

Performance Statistics

	Value
Assigned Value	2,688 µg/g
Uncertainty of Assigned Value	270 µg/g
SDPA	611 µg/g
Expanded SDPA	668.0 µg/g
Satisfactory Range	1,352 to 4,024 µg/g
Satisfactory z' scores	75.0%
Questionable z' scores	0.0%
Unsatisfactory z' scores	25.0%

Good agreement was observed between the participant median result and the theoretical spike values, particularly for the class 1 solvents, which have allowable concentrations in pharmaceutical products of <10ppm.

Table 1: Comparison of the participant median result and the theoretical spike values in PHARMASSURE round 60.

Parameter	Spike value (µg/g)	Median (µg/g)
Benzene	1.60	1.62
Carbon tetrachloride	5.36	8.43
1,2-Dichloroethane	8.24	8.44
1,1-Dichloroethene	-	-
1,1,1-Trichloroethane	1281	1214

Conclusions

A feature of the residual solvent sample was a number of 'non-analytical' errors and truncated 'less than' results in the analytical data returned. Future developments to eliminate such data and the addition of 'incurred, residual solvent' matrix samples to the PHARMASSURE scheme is in progress for the next scheme year.

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