PRACTICAL APPLICATIONS TO USP <467> IMPLEMENTATION

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WHAT ARE RESIDUAL SOLVENTS?

Organic volatile impurities (OVIs), commonly referred to as residual solvents, are organic volatile chemicals used or produced in the manufacturing of drug substances and excipients, or in the preparation of drug products. Residual solvents refer to impurities that are not removed during the product purification, or possibly formed during packaging or storage.

Drug manufacturers have to ensure that theses impurities are removed or are present only in limited concentration for toxicological concerns. The acceptable level of residual solvents has been established by the International Conference on Harmonization (ICH Q3C). On July 1, 2008, the United States Pharmacopeia (USP) implemented a new test requirement for the control of residual solvents in drug products (USP 30 NF 25). This new requirement, known has a General Chapter <467> designated under "Residual Solvents", replaced the previous USP General Chapter <467> designated under "Organic Volatile Impurities". Therefore, the US Food and Drug Administration (FDA) requires that US-marketed drug products, with a USP monograph, meet the residual solvents requirements in the revised General Chapter <467>.

HOW ARE RESIDUAL SOLVENTS CLASSIFIED?

Residual solvents are classified into 3 classes based on risk assessment. Class 1 (Residual Solvents) represents "solvents to be avoided". These solvents are known to be human carcinogens, strongly suspected human carcinogens and environmental hazards. Nevertheless, USP allows their use with justification. Levels must be routinely tested if the solvents are likely to be present in either intermediates, final active substances or final drug product even though the amount is lower than the acceptable level. Class 2 (Residual Solvents, where PDE is the permitted daily exposure) are described as "solvents to be limited". These solvents are non-genotoxic animal carcinogens or possible causative agents

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

of other irreversible toxicity such as neurotoxicity or teratogenicity. They are also suspected of other significant but irreversible toxicities. Solvents with Low Toxic Potential to Man fall into Class 3 (Residual Solvents). For these solvents, no health-based exposure limit is needed. Finally, there are ten additional compounds have been identified but not classified due to insufficient toxicological data.

TABLE 3: CLASS 3 RESIDUAL SOLVENTS[3]

RESIDUAL SOLVENT
Acetic acid
Acetone
Anisole
1-Butanol
2-Butanol
Butyl acetate
Tert-Butylmethyl ether
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

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

WHAT IS THE IMPACT FOR THE PHARMACEUTICAL INDUSTRY?

The first challenge for pharmaceutical manufacturers is acquiring all the necessary information to establish the residual solvents likely to be present in their raw materials (drug substances and excipients). The information would need to be verified by analytical testing. These analytical test represent the second challenge for pharmaceutical manufacturers. Moreover, when changing excipients sources, pharmaceutical manufacturers must consider whether changes of this kind may have an impact on residual solvents.

WHAT IS THE COMPENDIA TESTING METHODOLOGY?

The revised USP<467> method consists of a static headspace extraction, hyphenated with a gas chromatographic separation system and a flame ionization detection. The method is divided into two separate sections based upon sample solubility and referred to:

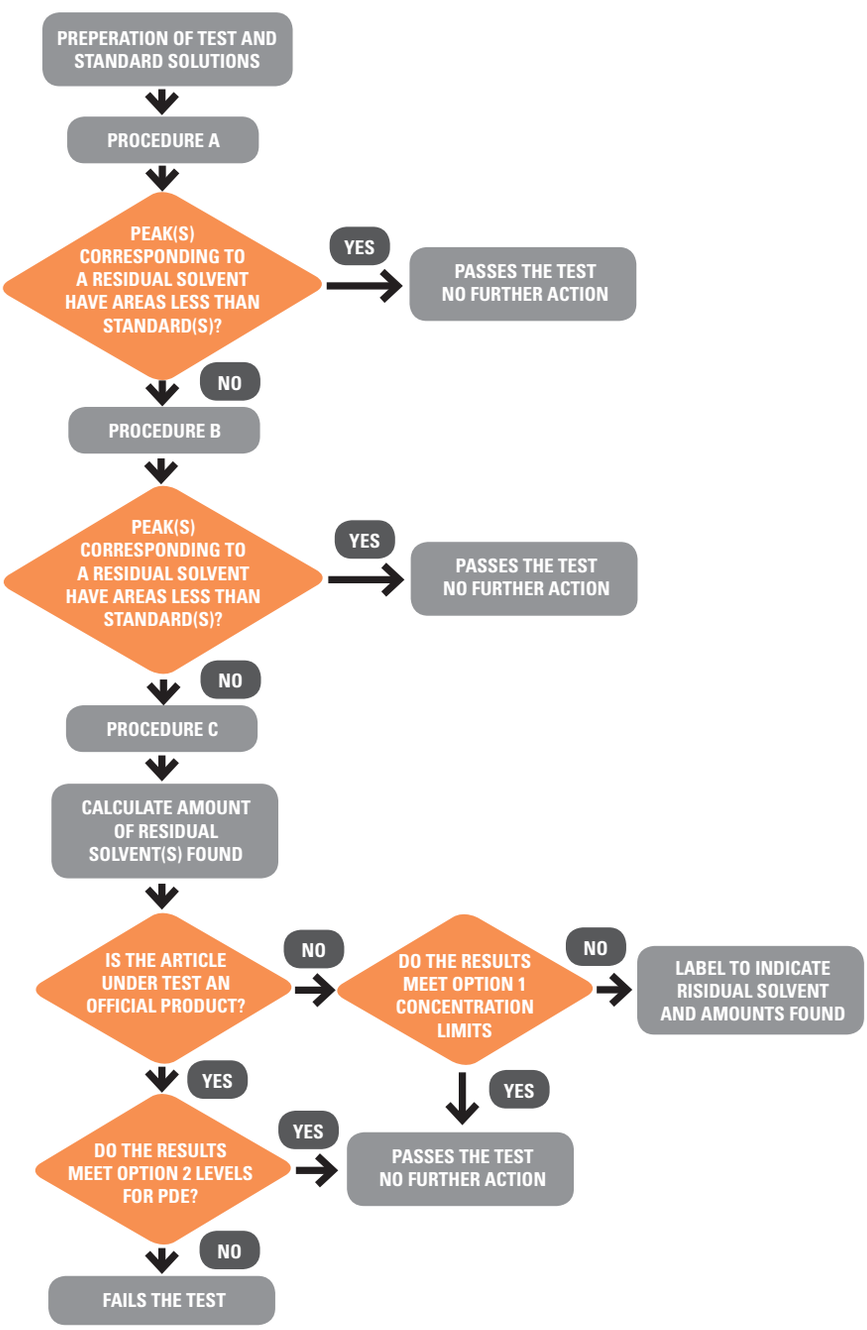
- Water-soluble articles
- Water-insoluble articles

The methodology for both types of articles is similar and consists of three procedures:

- Procedure A for identification and limit test
- Procedure B for confirmatory test
- Procedure C for quantitative test

The Testing methodology decision tree, as described in USP <467>, is shown in Figure 1.

FIGURE 1: TESTING METHODOLOGY DECISION TREE[4]



PROCEDURE A

Procedure A is performed on a G43 capillary column. A system suitability test must be performed to verify the operating conditions and is based on:

- Signal-to-noise ratio (S/N) of 1,1,1-Trichloroethane in the Class 1 Standard Solution which should be greater than 5,
- Signal-to-noise ratio (S/N) of all peaks in the Class 1 System Suitability Solution should not be less than 3,
- Resolution between acetonitrile and methylene chloride in the Class 2 Mixture A Standard Solution should not be less than 1.

If the system suitability test meets those requirements, the test solutions are assayed along with Class 1, Class 2 Mixture A and B, as described in the compendia, and Class 3 Standard Solutions. The Class 3 Standard Solutions should be prepared by the laboratory performing the test since no mixture is available.

If a peak response of any peak in the test solution is greater than or equal to a corresponding peak in either Class 1, Class 2 Mixture A and B, and Class 3 Standard Solutions, then Procedure B has to be performed to verify the identity of the peak. Otherwise the article meets the requirements of this test.

Nevertheless, if Class 1 residual solvents are identified, they should be quantified even if the amount is lower than the acceptable level.

FIGURE 2: CLASS 1 STANDARD SOLUTION CHROMATOGRAM

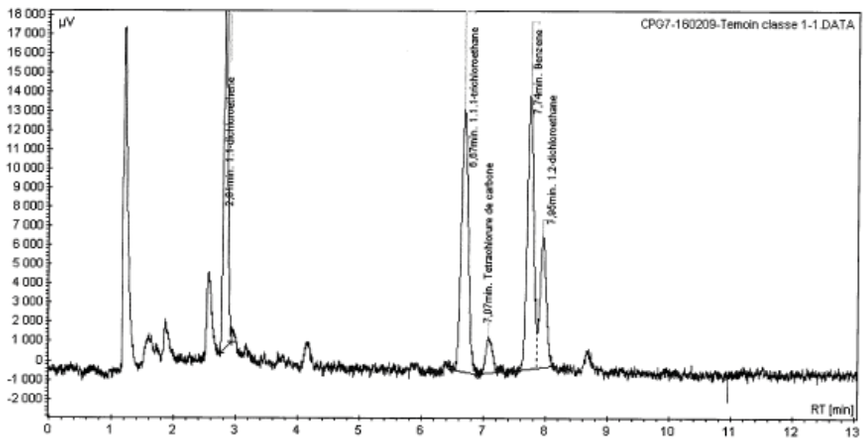


FIGURE 3: CLASS 2 MIXTURE A STANDARD SOLUTION CHROMATOGRAM

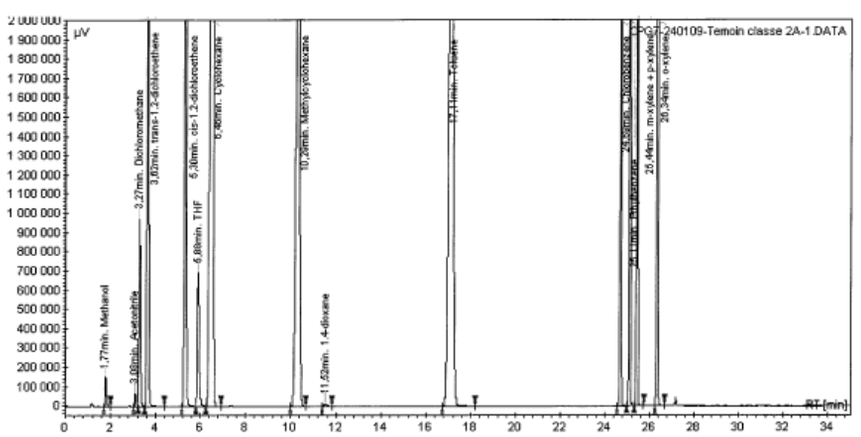
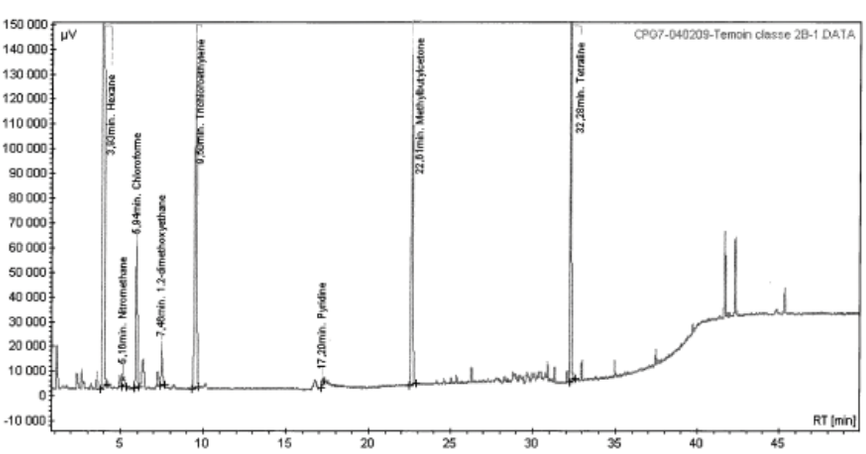


FIGURE 4: CLASS 2 MIXTURE B STANDARD SOLUTION CHROMATOGRAM



PROCEDURE B

Procedure B is performed to confirm the analyte identity on a G16 capillary column. The same standard solutions and system suitability solution are used but the acceptable criteria differ for the verification of the operating conditions. Indeed, the system suitability is based on:

- Signal-to-noise ratio (S/N) of benzene in the Class 1 Standard Solution which should be greater than 5,
- Signal-to-noise ratio (S/N) of all peaks in the Class 1 System Suitability Solution should not be less than 3,
- Resolution between acetonitrile and cis-dichloroethene in the Class 2 Mixture A Standard Solution should not be less than 1.

If the system suitability test meets those requirements, the test solutions are assayed along with Class 1, Class 2 Mixture A and B, and Class 3 Standard Solutions.

If the peak response(s) in the test solution for the peak identified in procedure A is/are greater than or equal to a corresponding peak(s) in either the Class 1, Class 2 Mixture A and B, and Class 3 Standard Solutions, then Procedure C has to be performed to quantify the peak(s). Otherwise the article meets the requirements of this test.

PROCEDURE C

Procedure C has the same operating conditions as Procedure A. Individual standards are prepared by dilution of the respective USP residual solvents reference standard. The quantification is achieved by the analysis of a spiked test solution. The operating conditions of Procedure B could be used if more relevant.

WHAT ARE THE LIMITATIONS OF THE NEW COMPENDIA TESTING METHODOLOGY?

As suggested by the USP, six important Class 2 residual solvents are not volatile enough for headspace testing (Table 4: Residual Solvents to be Analysed by Direct Injection). This issue is overcome by a direct injection, but the method has to be validated. An additional technical issue concerns the analysis of formic acid (Class 3 residual solvent). This analyte can not be analysed by gas chromatography.

An alternative method consists of an HPLC method with post-column derivatization. As mentioned previously, this method has to be validated. The system suitability criteria can be difficult to achieve regarding the signal-to-noise ratio for carbon tetrachloride. Using head space injection, there is a low response of this analyte due to a high partition coefficient (K). This K factor can be optimized by:

- Addition of salts
- Changing the dilution solvent
- Changing the heating temperature
- Reducing the solvent volume

Nevertheless any change to the compendia method must be validated.

CONCLUSION

The implementation of this new general chapter USP<467> Residual Solvents is a real challenge for pharmaceutical manufacturers. The tests are product-specific and require analytical method verification or analytical method development and validation. This analytical work is time consuming and requires planning and competent scientific staff. A reasonable alternative to developing, validating, and testing is to outsource. Contract testing laboratories must meet the needs of many clients and their extensive residual solvent testing requirements. The wide breadth of experience that contract laboratories bring make them an ideal partner for pharmaceutical companies striving to meet the new USP requirements for residual solvents.

REFERENCES:

1. *USP 32, General Chapter <467>, Table 1, May 2009*
2. *USP 32, General Chapter <467>, Table 2, May 2009*
3. *USP 32, General Chapter <467>, Table 3, May 2009*
4. *USP 32, General Chapter <467>, Figure 1, May 2009*

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