During the manufacturing of actives or excipients, or during the preparation of medicinal products, solvents that are used may not be completely removed. These solvents may have harmful effects on human health or on the environment and must be removed to the maximum extent possible. ICH’s Q3C guide (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) establishes the acceptable levels of residual solvents in pharmaceuticals and classifies them according to their toxicity (see Tables 1, 2 and 3).

It also describes the official methods for content analysis of said solvents in actives, excipients and/or medicines. The European Pharmacopoeia and the USP have adopted these same guidelines (Ph. Eur. method 2.4.24 and USP <467>).

The method normally consists of dissolving the sample in an appropriate solvent (water, dimethyl sulfoxide or dimethyl formamide, among others) to remove the residual solvent. Subsequent analysis is done by Headspace Gas Chromatography.

Therefore it is important that the solvent to be used for dissolving the sample has maximum purity and contains none of the residual solvents to be analyzed. At PanReac AppliChem we are experts on solvent purification and control; we offer three of the most frequently used solvents in the preparation of samples for subsequent analysis by Headspace Gas Chromatography. To ensure the utmost quality of these new solvents it has been necessary to develop new, more demanding manufacturing and packaging protocols.

<table>
<thead>
<tr>
<th>Product</th>
<th>Assay (min.)</th>
<th>Code</th>
<th>Pack.</th>
</tr>
</thead>
<tbody>
<tr>
<td>N,N-Dimethylacetamide</td>
<td>99,9 %</td>
<td>753145.1611</td>
<td>1000 ml</td>
</tr>
<tr>
<td></td>
<td></td>
<td>753145.1612</td>
<td>2,5 L</td>
</tr>
<tr>
<td>N,N-Dimethylformamide</td>
<td>99,9 %</td>
<td>751785.1611</td>
<td>1000 ml</td>
</tr>
<tr>
<td></td>
<td></td>
<td>751785.1612</td>
<td>2,5 L</td>
</tr>
<tr>
<td>Dimethyl Sulfoxide</td>
<td>99,9 %</td>
<td>751954.1611</td>
<td>1000 ml</td>
</tr>
<tr>
<td></td>
<td></td>
<td>751954.1612</td>
<td>2,5 L</td>
</tr>
</tbody>
</table>
Solvents for GC-Headspace

According to their risk to human health, residual solvents have been grouped into 3 categories:

**Class 1:** Solvents that should be avoided.
**Class 2:** Solvents to be limited.
**Class 3:** Solvents with low toxic potential.

In the following tables, solvents classified into the 3 categories show their permitted limit concentrations and the concentrations typically found of residual solvents in our GC-Headspace grade solvents.

### Table 1. Class 1 solvents.
(should be avoided)

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Concentration limit (ppm)</th>
<th>Type concentration in GC-Headspace grade (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzene</td>
<td>2</td>
<td>&lt; 0.5</td>
</tr>
<tr>
<td>Carbon tetrachloride</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>1,2-Dichloroethane</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>1,1-Dichloroethene</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>1,1,1-Trichloroethane</td>
<td>1500</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2. Class 2 solvents
(should be limited)

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Concentration limit (ppm)</th>
<th>Type concentration in GC-Headspace grade (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetonitrile</td>
<td>410</td>
<td></td>
</tr>
<tr>
<td>Chlorobenzene</td>
<td>360</td>
<td></td>
</tr>
<tr>
<td>Chloroform</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>Cyclohexane</td>
<td>3880</td>
<td></td>
</tr>
<tr>
<td>1,2-Dichloroethene</td>
<td>1870</td>
<td></td>
</tr>
<tr>
<td>Methylene chloride</td>
<td>600</td>
<td></td>
</tr>
<tr>
<td>1,2-Dimethoxyethane</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>N,N-Dimethylacetamide</td>
<td>1090</td>
<td></td>
</tr>
<tr>
<td>N,N-Dimethylformamide</td>
<td>880</td>
<td></td>
</tr>
<tr>
<td>1,4-Dioxiane</td>
<td>380</td>
<td></td>
</tr>
<tr>
<td>2-Ethoxyethanol</td>
<td>180</td>
<td></td>
</tr>
<tr>
<td>Ethylene glycol</td>
<td>620</td>
<td></td>
</tr>
<tr>
<td>Formamide</td>
<td>220</td>
<td></td>
</tr>
<tr>
<td>Hexane</td>
<td>290</td>
<td></td>
</tr>
<tr>
<td>Methanol</td>
<td>3000</td>
<td></td>
</tr>
<tr>
<td>2-Methoxyethanol</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Methyl butyl ketone</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Methyl cyclohexane</td>
<td>1180</td>
<td></td>
</tr>
<tr>
<td>N-Methylpyrrolidone</td>
<td>530</td>
<td></td>
</tr>
<tr>
<td>Nitromethane</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Pyridine</td>
<td>200</td>
<td></td>
</tr>
<tr>
<td>Sulfolane</td>
<td>160</td>
<td></td>
</tr>
<tr>
<td>Tetrahydrofuran</td>
<td>720</td>
<td></td>
</tr>
<tr>
<td>Tetralin</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Toluene</td>
<td>890</td>
<td></td>
</tr>
<tr>
<td>Trichloroethylene</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>Xylene</td>
<td>2170</td>
<td></td>
</tr>
</tbody>
</table>

### Table 3. Class 3 solvents.
(low toxic potential)

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Accepted limit concentration (ppm)</th>
<th>Type concentration in GC-Headspace grade (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetic acid</td>
<td>5,000</td>
<td></td>
</tr>
<tr>
<td>Acetone</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Anisole</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>1-Butanol</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>2-Butanol</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Butyl acetate</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>tert-Butyl methyl ether</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Cumene</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Dimethyl sulfoxide</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Ethanol</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Ethyl acetate</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Ethyl ether</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Ethyl formate</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Formic acid</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Heptane</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Isobutyl acetate</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Isopropyl acetate</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Methyl acetate</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>3-Methyl-1-butanol</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Methyl ethyl ketone</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Methyl isobutyl ketone</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>2-Methyl-1-propanol</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Pentane</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>1-Pentanol</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>1-Propanol</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>2-Propanol</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Propyl acetate</td>
<td>25</td>
<td></td>
</tr>
</tbody>
</table>
Technique
Figures 1, 2 and 3 show the chromatograms obtained for PanReac AppliChem HPLC-grade dimethyl sulfoxide (DMSO), N,N-dimethyl formamide (DMF) and N,N-dimethyl acetamide (DMA) compared to the GC-Headspace grade solvents.
The chromatographic conditions used are described in Table 4.

Table 4. Chromatographic conditions

<table>
<thead>
<tr>
<th>Gas Chromatograph</th>
<th>Headspace</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injector temperature</td>
<td>160ºC</td>
</tr>
<tr>
<td>Split ratio</td>
<td>5:1</td>
</tr>
<tr>
<td>Carrier gas</td>
<td>Helium</td>
</tr>
<tr>
<td>Carrier flow</td>
<td>1.5 mL/min</td>
</tr>
<tr>
<td>GC oven program</td>
<td>Initial temperature: 35 ºC</td>
</tr>
<tr>
<td></td>
<td>Initial time: 20 min</td>
</tr>
<tr>
<td></td>
<td>Rate: 25 ºC/min</td>
</tr>
<tr>
<td></td>
<td>Final temperature: 250 ºC</td>
</tr>
<tr>
<td></td>
<td>Final time: 10 min</td>
</tr>
<tr>
<td>Column</td>
<td>30 m x 0.25 mm x 1.4 μm DB-624, part# 122-1334</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Headspace</td>
<td></td>
</tr>
<tr>
<td>Loop size</td>
<td>1 mL</td>
</tr>
<tr>
<td>Headspace oven</td>
<td>85ºC</td>
</tr>
<tr>
<td>Loop temperature</td>
<td>100ºC</td>
</tr>
<tr>
<td>Transfer line temperature</td>
<td>120ºC</td>
</tr>
<tr>
<td>Equilibration time</td>
<td>30 min., high shake</td>
</tr>
<tr>
<td>Vial pressurization time</td>
<td>0.15 min.</td>
</tr>
<tr>
<td>Vent (loop fill time)</td>
<td>0.2 min.</td>
</tr>
<tr>
<td>Inject</td>
<td>0.5 min.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MS Detector</th>
<th>Reference standards</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synchronous SIM/scan mode on</td>
<td>USP Mixture Class 1</td>
</tr>
<tr>
<td>Scan</td>
<td>1601102</td>
</tr>
<tr>
<td>Source temperature</td>
<td>USP Mixture Class 2 Mix. A</td>
</tr>
<tr>
<td>Quad temperature</td>
<td>1601281</td>
</tr>
<tr>
<td></td>
<td>USP Mixture Class 2 Mix. B</td>
</tr>
<tr>
<td></td>
<td>1601292</td>
</tr>
</tbody>
</table>
In figures 4, 5 and 6, chromatograms obtained for PanReac AppliChem GC-Headspace grade dimethyl sulfoxide, dimethyl formamide and dimethyl acetamide are compared to those from different competitors. The chromatographic conditions used are described in Table 4.