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# Q3C — Tables and List

## Guidance for Industry

**U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)  
Center for Biologics Evaluation and Research (CBER)**

**August 2018  
ICH**

**Revision 4**

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## **Q3C — Tables and List Guidance for Industry<sup>1</sup>**

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

### **I. INTRODUCTION**

This is the companion document for the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidance for industry *Q3C Impurities: Residual Solvents*, which makes recommendations as to what amounts of residual solvents are considered safe in pharmaceuticals.

This document may be updated if proposals for change are submitted to the ICH Secretariat for consideration by the ICH Q3C Expert Working Group (EWG). If the EWG supports the proposal for change, the proposal will be submitted to the ICH Assembly for endorsement. Any proposals that are endorsed by the ICH Assembly will be announced through a notice in the *Federal Register* prior to the updating of this document. The guidance was revised in November 2003 to reflect updated recommendations for N-Methylpyrrolidone and Tetrahydrofuran; in February 2012 to reflect an updated recommendation for cumene; in October 2016 to reflect updated recommendations for Triethylamine and Methylisobutylketone; and in August 2018 to correct the permitted daily exposure (PDE) and concentration limit for Ethyleneglycol (see Table 2 on page 6), per the correct value calculated in Appendix 5.

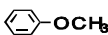



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
<sup>1</sup> This document was developed within the Expert Working Group (Quality) of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and has been subject to consultation by the regulatory parties, in accordance with the ICH process. This document was endorsed by the ICH Steering Committee at *Step 4* of the ICH process in July 1997. At *Step 4* of the process, the final draft is recommended for adoption to the regulatory agencies. This guidance was published in the *Federal Register* on December 24, 1997 (62 FR 67377), and is applicable to drug and biological products.

*Contains Nonbinding Recommendations*








**II. LIST OF SOLVENTS INCLUDED IN THE Q3C GUIDANCE**

<b>Solvent</b>	<b>Other Names</b>	<b>Structure</b>	<b>Class</b>
Acetic acid	Ethanoic acid	$\text{CH}_3\text{COOH}$	Class 3
Acetone	2-Propanone Propan-2-one	$\text{CH}_3\text{COCH}_3$	Class 3
Acetonitrile		$\text{CH}_3\text{CN}$	Class 2
Anisole	Methoxybenzene		Class 3
Benzene	Benzol		Class 1
1-Butanol	n-Butyl alcohol Butan-1-ol	$\text{CH}_3(\text{CH}_2)_3\text{OH}$	Class 3
2-Butanol	<i>sec</i> -Butyl alcohol Butan-2-ol	$\text{CH}_3\text{CH}_2\text{CH}(\text{OH})\text{CH}_3$	Class 3
Butyl acetate	Acetic acid butyl ester	$\text{CH}_3\text{COO}(\text{CH}_2)_3\text{CH}_3$	Class 3
<i>tert</i> -Butylmethylether	2-Methoxy-2-methyl-propane	$(\text{CH}_3)_3\text{COCH}_3$	Class 3
Carbon tetrachloride	Tetrachloromethane	$\text{CCl}_4$	Class 1
Chlorobenzene			Class 2
Chloroform	Trichloromethane	$\text{CHCl}_3$	Class 2
Cumene	Isopropylbenzene (1-Methyl)ethylbenzene	$\text{C}_6\text{H}_5\text{-CH}(\text{CH}_3)_2$	Class 2
Cyclohexane	Hexamethylene		Class 2
1,2-Dichloroethane	<i>sym</i> -Dichloroethane Ethylene dichloride Ethylene chloride	$\text{CH}_2\text{ClCH}_2\text{Cl}$	Class 1
1,1-Dichloroethene	1,1-Dichloroethylene Vinylidene chloride	$\text{H}_2\text{C=CCl}_2$	Class 1
1,2-Dichloroethene	1,2-Dichloroethylene Acetylene dichloride	$\text{ClHC=CHCl}$	Class 2

***Contains Nonbinding Recommendations***

Dichloromethane	Methylene chloride	$\text{CH}_2\text{Cl}_2$	Class 2
1,2-Dimethoxyethane	Ethyleneglycol dimethylether Monoglyme Dimethyl Cellosolve	$\text{H}_3\text{COCH}_2\text{CH}_2\text{OCH}_3$	Class 2
N,N-Dimethylacetamide	DMA	$\text{CH}_3\text{CON}(\text{CH}_3)_2$	Class 2
N,N-Dimethylformamide	DMF	$\text{HCON}(\text{CH}_3)_2$	Class 2
Dimethylsulfoxide	Methylsulfinylmethane Methyl sulfoxide DMSO	$(\text{CH}_3)_2\text{SO}$	Class 3
1,4-Dioxane	p-Dioxane [1,4]Dioxane		Class 2
Ethanol	Ethyl alcohol	$\text{CH}_3\text{CH}_2\text{OH}$	Class 3
2-Ethoxyethanol	Cellosolve	$\text{CH}_3\text{CH}_2\text{OCH}_2\text{CH}_2\text{OH}$	Class 2
Ethyl acetate	Acetic acid ethylester	$\text{CH}_3\text{COOCH}_2\text{CH}_3$	Class 3
Ethyleneglycol	1,2-Dihydroxyethane 1,2-Ethanediol	$\text{HOCH}_2\text{CH}_2\text{OH}$	Class 2
Ethylether	Diethyl ether Ethoxyethane 1,1'-Oxybisethane	$\text{CH}_3\text{CH}_2\text{OCH}_2\text{CH}_3$	Class 3
Ethyl formate	Formic acid ethylester	$\text{HCOOCH}_2\text{CH}_3$	Class 3
Formamide	Methanamide	$\text{HCONH}_2$	Class 2
Formic acid		$\text{HCOOH}$	Class 3
Heptane	n-Heptane	$\text{CH}_3(\text{CH}_2)_5\text{CH}_3$	Class 3
Hexane	n-Hexane	$\text{CH}_3(\text{CH}_2)_4\text{CH}_3$	Class 2
Isobutyl acetate	Acetic acid isobutylester	$\text{CH}_3\text{COOCH}_2\text{CH}(\text{CH}_3)_2$	Class 3
Isopropyl acetate	Acetic acid isopropylester	$\text{CH}_3\text{COOCH}(\text{CH}_3)_2$	Class 3
Methanol	Methyl alcohol	$\text{CH}_3\text{OH}$	Class 2
2-Methoxyethanol	Methyl Cellosolve	$\text{CH}_3\text{OCH}_2\text{CH}_2\text{OH}$	Class 2
Methyl acetate	Acetic acid methylester	$\text{CH}_3\text{COOCH}_3$	Class 3
3-Methyl-1-butanol	Isoamyl alcohol Isopentyl alcohol 3-Methylbutan-1-ol	$(\text{CH}_3)_2\text{CHCH}_2\text{CH}_2\text{OH}$	Class 3
Methylbutyl ketone	2-Hexanone	$\text{CH}_3(\text{CH}_2)_3\text{COCH}_3$	Class 2

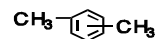
*Contains Nonbinding Recommendations*

	Hexan-2-one		
Methylcyclohexane	Cyclohexylmethane		Class 2
Methylethylketone	2-Butanone MEK Butan-2-one	$\text{CH}_3\text{CH}_2\text{COCH}_3$	Class 3
Methylisobutylketone	4-Methylpentan-2-one 4-Methyl-2-pentanone MIBK	$\text{CH}_3\text{COCH}_2\text{CH}(\text{CH}_3)_2$	Class 2
2-Methyl-1-propanol	Isobutyl alcohol 2-Methylpropan-1-ol	$(\text{CH}_3)_2\text{CHCH}_2\text{OH}$	Class 3
N-Methylpyrrolidone	1-Methylpyrrolidin-2-one 1-Methyl-2-pyrrolidinone		Class 2
Nitromethane		$\text{CH}_3\text{NO}_2$	Class 2
Pentane	n-Pentane	$\text{CH}_3(\text{CH}_2)_3\text{CH}_3$	Class 3
1-Pentanol	Amyl alcohol Pentan-1-ol Pentyl alcohol	$\text{CH}_3(\text{CH}_2)_3\text{CH}_2\text{OH}$	Class 3
1-Propanol	Propan-1-ol Propyl alcohol	$\text{CH}_3\text{CH}_2\text{CH}_2\text{OH}$	Class 3
2-Propanol	Propan-2-ol Isopropyl alcohol	$(\text{CH}_3)_2\text{CHOH}$	Class 3
Propylacetate	Acetic acid propylester	$\text{CH}_3\text{COOCH}_2\text{CH}_2\text{CH}_3$	Class 3
Pyridine			Class 2
Sulfolane	Tetrahydrothiophene 1,1-dioxide		Class 2
Tetrahydrofuran	Tetramethylene oxide Oxacyclopentane		Class 2
Tetralin	1,2,3,4-Tetrahydro-naphthalene		Class 2
Toluene	Methylbenzene		Class 2
1,1,1-Trichloroethane	Methylchloroform	$\text{CH}_3\text{CCl}_3$	Class 1
1,1,2-Trichloroethene	Trichloroethene	$\text{HC}(\text{Cl})=\text{CCl}_2$	Class 2
Triethylamine	N,N-Diethylethanamine	$\text{N}(\text{CH}_2\text{CH}_3)_3$	Class 3

## Contains Nonbinding Recommendations

Xylene<sup>1</sup>

Dimethylbenzene  
Xylol



Class 2

<sup>1</sup>Usually 60% m-xylene, 14% p-xylene, 9% o-xylene with 17% ethylbenzene.

### III. SOLVENTS GROUPED BY CLASS

Solvents in Class 1 (Table 1) should not be employed in the manufacture of drug substances, excipients, and drug products because of their unacceptable toxicity or their deleterious environmental effect. However, if their use is unavoidable in order to produce a drug product with a significant therapeutic advance, then their levels should be restricted as shown in Table 1, unless otherwise justified. The solvent 1,1,1-Trichloroethane is included in Table 1 because it is an environmental hazard. The stated limit of 1,500 ppm is based on a review of the safety data.

**Table 1. – Class 1 Solvents in Pharmaceutical Products (Solvents That Should Be Avoided)**

Solvent	Concentration Limit (ppm)	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	1,500	Environmental hazard

### *Contains Nonbinding Recommendations*

Solvents in Class 2 (Table 2) should be limited in pharmaceutical products because of their inherent toxicity. PDEs are given to the nearest 0.1 mg/day, and concentrations are given to the nearest 10 ppm. The stated values do not reflect the necessary analytical precision of determination. Precision should be determined as part of the validation of the method.

**Table 2. – Class 2 Solvents in Pharmaceutical Products**

<b>Solvent</b>	<b>PDE (mg/day)</b>	<b>Concentration Limit (ppm)</b>
Acetonitrile	4.1	410
Chlorobenzene	3.6	360
Chloroform	0.6	60
Cyclohexane	38.8	3,880
Cumene	0.7	70
1,2-Dichloroethene	18.7	1,870
Dichloromethane	<del>18.7</del> 6.0	600
1,2-Dimethoxyethane	1.0	100
N,N-Dimethylacetamide	10.9	1,090
N,N-Dimethylformamide	8.8	880
1,4-Dioxane	3.8	380
2-Ethoxyethanol	1.6	160
Ethyleneglycol	3.1	310
Formamide	2.2	220
Hexane	2.9	290
Methanol	30.0	3,000
2-Methoxyethanol	0.5	50
Methylbutylketone	0.5	50
Methylcyclohexane	11.8	1,180
Methylisobutylketone <sup>2</sup>	45	4,500
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

<sup>2</sup> The information included for Methylisobutylketone reflects that included in the *Revision of PDE Information for Methylisobutylketone*, which reached *Step 4* in November 2016 and was subsequently incorporated into the core guidance.



### *Contains Nonbinding Recommendations*

Toluene	8.9	890
1,1,2-Trichloroethene	0.8	80
Xylene <sup>1</sup>	21.7	2,170

<sup>1</sup>Usually 60% m-xylene, 14% p-xylene, 9% o-xylene with 17% ethylbenzene.

Solvents in Class 3 (Table 3) may be regarded as less toxic and of lower risk to human health. Class 3 includes no solvent known as a human health hazard at levels normally accepted in pharmaceuticals. However, there are no long-term toxicity or carcinogenicity studies for many of the solvents in Class 3. Available data indicate that they are less toxic in acute or short-term studies and negative in genotoxicity studies. It is considered that amounts of these residual solvents of 50 mg per day or less (corresponding to 5,000 ppm or 0.5 percent under Option 1) would be acceptable without justification. Higher amounts may also be acceptable provided they are realistic in relation to manufacturing capability and good manufacturing practice (GMP).

**Table 3. – Class 3 Solvents Which Should Be Limited by GMP or Other Quality-Based Requirements**

Acetic acid	Heptane
Acetone	Isobutylacetate
Anisole	Isopropylacetate
1-Butanol	Methylacetate
2-Butanol	3-Methyl-1-butanol
Butylacetate	Methylethylketone
<i>tert</i> -Butylmethylether	2-Methyl-1-propanol
Dimethylsulfoxide	Pentane
Ethanol	1-Pentanol
Ethylacetate	1-Propanol
Ethylether	2-Propanol
Ethylformate	Propylacetate
Formic acid	Triethylamine <sup>3</sup>

<sup>3</sup> The information included for Triethylamine reflects that included in the *Revision of PDE Information for Triethylamine*, which reached *Step 4* in November 2016 and was subsequently incorporated into the core guidance.

### *Contains Nonbinding Recommendations*

The solvents listed in Table 4 may also be of interest to manufacturers of excipients, drug substances, or drug products. However, no adequate toxicological data on which to base a PDE were found. Manufacturers should supply justification for residual levels of these solvents in pharmaceutical products.

**Table 4. – Solvents for Which No Adequate Toxicological Data Were Found**

1,1-Diethoxypropane	Methylisopropyl ketone
1,1-Dimethoxymethane	Methyltetrahydrofuran
2,2-Dimethoxypropane	Petroleum ether
Isooctane	Trichloroacetic acid
Isopropylether	Trifluoroacetic acid