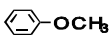






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






II. LIST OF SOLVENTS INCLUDED IN THE Q3C GUIDANCE

Solvent	Other Names	Structure	Class
Acetic acid	Ethanoic acid	CH_3COOH	Class 3
Acetone	2-Propanone Propan-2-one	CH_3COCH_3	Class 3
Acetonitrile		CH_3CN	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	CCl_4	Class 1
Chlorobenzene			Class 2
Chloroform	Trichloromethane	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	ClHC=CHCl	Class 2

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Dichloromethane	Methylene chloride	CH_2Cl_2	Class 2
1,2-Dimethoxyethane	Ethyleneglycol dimethyl ether 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
Dimethyl sulfoxide	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	HCONH_2	Class 2
Formic acid		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	CH_3OH	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

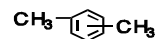
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	Hexan-2-one		
Methylcyclohexane	Cyclohexylmethane		Class 2
Methylethylketone	2-Butanone MEK Butan-2-one	$\text{CH}_3\text{CH}_2\text{COCH}_3$	Class 3
Methylisobutylketone	4-Methylpentan-2-one 4-Methyl-2-pentanone MIBK	$\text{CH}_3\text{COCH}_2\text{CH}(\text{CH}_3)_2$	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		CH_3NO_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	CH_3CCl_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

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Xylene¹

Dimethylbenzene
Xylol



Class 2

¹Usually 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

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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

Solvent	PDE (mg/day)	Concentration Limit (ppm)
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	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
Methylbutyl ketone	0.5	50
Methylcyclohexane	11.8	1,180
Methylisobutylketone ²	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

² 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.

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Toluene	8.9	890
1,1,2-Trichloroethene	0.8	80
Xylene ¹	21.7	2,170

¹Usually 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 ³

³ 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.

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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

