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

Q3C — Tables and List

Guidance for Industry

Additional copies are available from:
Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov
https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm
or
Office of Communication, Outreach and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, Room 3128
Silver Spring, MD 20993-0002
Phone: 800-835-4709 or 240-402-8010
Email: ocod@fda.hhs.gov
https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

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

Contains Nonbinding Recommendations

Q3C — Tables and List
Guidance for Industry[1]

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

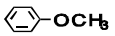
This is the companion document for the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidance for industry *Q3C Impurities: Residual Solvents*, which makes recommendations as to what amounts of residual solvents are considered safe in pharmaceuticals.

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.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

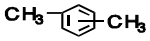
[1] This document was developed within the Expert Working Group (Quality) of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and has been subject to consultation by the regulatory parties, in accordance with the ICH process. This document 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.

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	$CH_3(CH_2)_3OH$	Class 3
2-Butanol	*sec*-Butyl alcohol Butan-2-ol	$CH_3CH_2CH(OH)CH_3$	Class 3
Butyl acetate	Acetic acid butyl ester	$CH_3COO(CH_2)_3CH_3$	Class 3
tert-Butylmethyl ether	2-Methoxy-2-methyl-propane	$(CH_3)_3COCH_3$	Class 3
Carbon tetrachloride	Tetrachloromethane	CCl_4	Class 1
Chlorobenzene			Class 2
Chloroform	Trichloromethane	$CHCl_3$	Class 2
Cumene	Isopropylbenzene (1-Methyl)ethylbenzene	$C_6H_5\text{-}CH(CH_3)_2$	Class 2
Cyclohexane	Hexamethylene		Class 2
1,2-Dichloroethane	*sym*-Dichloroethane Ethylene dichloride Ethylene chloride	CH_2ClCH_2Cl	Class 1
1,1-Dichloroethene	1,1-Dichloroethylene Vinylidene chloride	$H_2C=CCl_2$	Class 1
1,2-Dichloroethene	1,2-Dichloroethylene Acetylene dichloride	$ClHC=CHCl$	Class 2

Dichloromethane	Methylene chloride	CH_2Cl_2	Class 2
1,2-Dimethoxyethane	Ethyleneglycol dimethyl ether Monoglyme Dimethyl Cellosolve	$H_3COCH_2CH_2OCH_3$	Class 2
N,N- Dimethylacetamide	DMA	$CH_3CON(CH_3)_2$	Class 2
N,N- Dimethylformamide	DMF	$HCON(CH_3)_2$	Class 2
Dimethyl sulfoxide	Methylsulfinylmethane Methyl sulfoxide DMSO	$(CH_3)_2SO$	Class 3
1,4-Dioxane	p-Dioxane [1,4]Dioxane		Class 2
Ethanol	Ethyl alcohol	CH_3CH_2OH	Class 3
2-Ethoxyethanol	Cellosolve	$CH_3CH_2OCH_2CH_2OH$	Class 2
Ethyl acetate	Acetic acid ethyl ester	$CH_3COOCH_2CH_3$	Class 3
Ethyleneglycol	1,2-Dihydroxyethane 1,2-Ethanediol	$HOCH_2CH_2OH$	Class 2
Ethyl ether	Diethyl ether Ethoxyethane 1,1'-Oxybisethane	$CH_3CH_2OCH_2CH_3$	Class 3
Ethyl formate	Formic acid ethyl ester	$HCOOCH_2CH_3$	Class 3
Formamide	Methanamide	$HCONH_2$	Class 2
Formic acid		$HCOOH$	Class 3
Heptane	n-Heptane	$CH_3(CH_2)_5CH_3$	Class 3
Hexane	n-Hexane	$CH_3(CH_2)_4CH_3$	Class 2
Isobutyl acetate	Acetic acid isobutyl ester	$CH_3COOCH_2CH(CH_3)_2$	Class 3
Isopropyl acetate	Acetic acid isopropyl ester	$CH_3COOCH(CH_3)_2$	Class 3
Methanol	Methyl alcohol	CH_3OH	Class 2
2-Methoxyethanol	Methyl Cellosolve	$CH_3OCH_2CH_2OH$	Class 2
Methyl acetate	Acetic acid methyl ester	CH_3COOCH_3	Class 3
3-Methyl-1-butanol	Isoamyl alcohol Isopentyl alcohol 3-Methylbutan-1-ol	$(CH_3)_2CHCH_2CH_2OH$	Class 3
Methylbutyl ketone	2-Hexanone	$CH_3(CH_2)_3COCH_3$	Class 2

	Hexan-2-one		
Methylcyclohexane	Cyclohexylmethane		Class 2
Methylethyl ketone	2-Butanone MEK Butan-2-one	$CH_3CH_2COCH_3$	Class 3
Methylisobutyl ketone	4-Methylpentan-2-one 4-Methyl-2-pentanone MIBK	$CH_3COCH_2CH(CH_3)_2$	Class 2
2-Methyl-1-propanol	Isobutyl alcohol 2-Methylpropan-1-ol	$(CH_3)_2CHCH_2OH$	Class 3
N-Methylpyrrolidone	1-Methylpyrrolidin-2-one 1-Methyl-2-pyrrolidinone		Class 2
Nitromethane		CH_3NO_2	Class 2
Pentane	n-Pentane	$CH_3(CH_2)_3CH_3$	Class 3
1-Pentanol	Amyl alcohol Pentan-1-ol Pentyl alcohol	$CH_3(CH_2)_3CH_2OH$	Class 3
1-Propanol	Propan-1-ol Propyl alcohol	$CH_3CH_2CH_2OH$	Class 3
2-Propanol	Propan-2-ol Isopropyl alcohol	$(CH_3)_2CHOH$	Class 3
Propyl acetate	Acetic acid propyl ester	$CH_3COOCH_2CH_2CH_3$	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	$HClC=CCl_2$	Class 2
Triethylamine	N,N-Diethylethanamine	$N(CH_2CH_3)_3$	Class 3

Xylene[1]	Dimethybenzene Xylol		Class 2

[1]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

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	18.7 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[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.

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

[1]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	Isobutyl acetate
Anisole	Isopropyl acetate
1-Butanol	Methyl acetate
2-Butanol	3-Methyl-1-butanol
Butyl acetate	Methylethyl ketone
tert-Butylmethyl ether	2-Methyl-1-propanol
Dimethyl sulfoxide	Pentane
Ethanol	1-Pentanol
Ethyl acetate	1-Propanol
Ethyl ether	2-Propanol
Ethyl formate	Propyl acetate
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.

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
Isopropyl ether	Trifluoroacetic acid