EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 January 2022
EMA/CVMP/VICH/502/1999
Committee for Medicinal Products for Veterinary Use (CVMP)

VICH GL18(R2) Impurities: residual solvents in new veterinary medicinal products, active substances and excipients (revision 2)

Draft

Draft agreed by VICH Steering Committee	December 2021
Adoption by CVMP for release for consultation	January 2022
Start of public consultation	31 January 2022
End of consultation (deadline for comments)	10 June 2022

Comments should be provided using this template. The completed comments form should be sent to vet-guidelines@ema.europa.eu

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International Cooperation on Harmonisation of Technical Requirements
for Registration of Veterinary Medicinal Products

VICH GL18(R2) (QUALITY) – IMPURITIES
December 2021
Revision at Step 9
For consultation at Step 4

IMPURITIES: RESIDUAL SOLVENTS IN NEW VETERINARY MEDICINAL PRODUCTS, ACTIVE SUBSTANCES AND EXCIPIENTS (REVISION 2)

Revision at Step 9

Recommended for Consultation at Step 4 of the VICH Process
in October 2019
by the VICH Steering Committee

This Guideline has been developed by the appropriate VICH Expert Working Group will be subject to consultation by the parties, in accordance with the VICH Process. At Step 7 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

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IMPURITIES: RESIDUAL SOLVENTS IN NEW VETERINARY MEDICINAL PRODUCTS, ACTIVE SUBSTANCES AND EXCIPIENTS (REVISION 2)

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1. INTRODUCTION

The objective of this guideline is to recommend acceptable amounts for residual solvents in pharmaceuticals for the safety of the target animal as well as for the safety of residues in products derived from treated food producing animals. The guideline recommends use of less toxic solvents and describes levels considered to be toxicologically acceptable for some residual solvents.

Residual solvents in pharmaceuticals are defined here as organic volatile chemicals that are used or produced in the manufacture of active substances or excipients, or in the preparation of veterinary medicinal products. The solvents are not completely removed by practical manufacturing techniques. Appropriate selection of the solvent for the synthesis of active substance may enhance the yield, or determine characteristics such as crystal form, purity, and solubility. Therefore, the solvent may sometimes be a critical parameter in the synthetic process. This guideline does not address solvents deliberately used as excipients nor does it address solvates. However, the content of solvents in such products should be evaluated and justified.

Since there is no therapeutic benefit from residual solvents, all residual solvents should be removed to the extent possible to meet product specifications, good manufacturing practices, or other quality-based requirements. Veterinary medicinal products should contain no higher levels of residual solvents than can be supported by safety data. Some solvents that are known to cause unacceptable toxicities (Class 1, Table 1) should be avoided in the production of active substances, excipients, or veterinary medicinal products unless their use can be strongly justified in a risk-benefit assessment. Some solvents associated with less severe toxicity (Class 2, Table 2) should be limited in order to protect target animals and human consumers from potential adverse effects. Ideally, less toxic solvents (Class 3, Table 3) should be used where practical. The complete list of solvents included in this guideline is given in Appendix 1.

The lists are not exhaustive and other solvents can be used and later added to the lists. Recommended limits of Class 1 and 2 solvents or classification of solvents may change, as new safety data becomes available. Supporting safety data in a marketing application for a new veterinary medicinal product containing a new solvent may be based on concepts in this guideline or the concept of qualification of impurities as expressed in the guideline for active substance (VICH GL 10, Impurities in New Veterinary Drug Substances) or veterinary medicinal product (VICH GL 11, Impurities in New Veterinary Medicinal Products), or all three guidelines.

2. SCOPE OF THE GUIDELINE

Residual solvents in active substances, excipients, and in veterinary medicinal products are within the scope of this guideline. Therefore, testing should be performed for residual solvents when production or purification processes are known to result in the presence of such solvents. It is only necessary to test for solvents that are used or produced in the manufacture or purification of medicinal substances, excipients, or veterinary medicinal products. Although manufacturers may choose to test the veterinary medicinal product, a cumulative method may be used to calculate the residual solvent levels in the product from the levels in the ingredients used to produce the product. If the calculation results in a level equal to or below that recommended in this guideline, no testing of the veterinary medicinal product for residual solvents need be considered. If, however, the calculated level is above the recommended level, the veterinary medicinal product should be tested to ascertain whether the formulation process has reduced the relevant solvent level to within the acceptable amount. The veterinary medicinal product should also be tested if a solvent is used during its manufacture. This guideline does not apply to potential new active substances, excipients, or veterinary medicinal products used during the clinical research stages of development, nor does it apply to existing marketed veterinary medicinal products.

The guideline applies to all dosage forms and routes of administration. Higher levels of residual solvents may be acceptable in certain cases or topical application. Justification for these levels should be made on a case by case basis.

See Appendix 2 for additional background information related to residual solvents.

3. GENERAL PRINCIPLES

3.1 Classification of Residual Solvents by Risk Assessment

The term "tolerable daily intake" (TDI) is used by the International Program on Chemical Safety (IPCS) to describe exposure limits of toxic chemicals and "acceptable daily intake" (ADI) is used by the World Health Organisation (WHO) and other national and international health authorities and institutes. The new term "permitted daily exposure" (PDE) is defined in the present guideline as a pharmaceutically acceptable intake of residual solvents to avoid confusion of differing values for ADIs of the same substance.

Residual solvents assessed in this guideline are listed in Appendix 1 by common names and structures. They were evaluated for their possible risk to human health and placed into one of three classes as follows:

Class 1 solvents: Solvents to be avoided

Known human carcinogens, strongly suspected human carcinogens, and environmental hazards.

Class 2 solvents: Solvents to be limited

Non-genotoxic animal carcinogens or possible causative agents of other irreversible toxicity such as neurotoxicity or teratogenicity.

Solvents suspected of other significant but reversible toxicities.

Class 3 solvents: Solvents with low toxic potential

Solvents with low toxic potential to man; no health-based exposure limit is needed. Class 3 solvents have PDEs of 50 mg or more per day.

3.2 Methods for Establishing Exposure Limits

The method used to establish permitted daily exposures for residual solvents is presented in Appendix 3. Summaries of the toxicity data that were used to establish limits are published in Pharmeuropa, Vol. 9, No. 1, Supplement, April 1997 and in Parts II to Part VI of the ICH Guideline on Impurities: Guideline for Residual Solvents (Q3C(R8)).

3.3 Options for Describing Limits of Class 2 Solvents

Three options are available when setting limits for Class 2 solvents.
Option 1: The concentration limits in ppm stated in Table 2 can be used. They were calculated using equation (1) below by assuming a product mass of 10 g administered daily.

$$(1)\ \text{Concentration (ppm)} = \frac{1000 \text{ x PDE}}{\text{dose}}$$

Here, PDE is given in terms of mg/day and dose is given in g/day.
These limits are considered acceptable for residual solvents in all substances, excipients, or products. Therefore this option may be applied if the daily dose is not known or fixed. If the residual solvents in all excipients and active substances in a formulation meet the limits given in Option 1, then these components may be used in any proportion. No further calculation is necessary provided the daily dose does not exceed 10 g. Products that are administered in doses greater than 10 g per day should be considered under Option 2.
Option 2: it is not considered necessary for residual solvents in each component of the veterinary medicinal product to comply with the limits given in Option 1. The PDE in terms of mg/day as stated in Table 2 can be used with the known maximum daily dose and equation (1) above to determine the concentration of residual solvent allowed in the veterinary medicinal product. Such limits are considered acceptable provided that it has been demonstrated that the residual solvent has been reduced to the practical minimum. The limits should be realistic in relation to analytical precision, manufacturing capability, reasonable variation in the manufacturing process, and the limits should reflect contemporary manufacturing standards.

Option 2 may be applied by adding the amounts of a residual solvent present in each of the components of the veterinary medicinal product. The sum of the amounts of solvent per day should be less than that given by the PDE.

Consider an example of the use of Option 1 and Option 2 applied to acetonitrile in a veterinary medicinal product. The permitted daily exposure to acetonitrile is 4.1 mg per day; thus, the Option 1 limit is 410 ppm. The maximum administered daily mass of a veterinary medicinal product is 5.0 g, and the veterinary medicinal product contains two excipients. The composition of the veterinary medicinal product and the calculated maximum content of residual acetonitrile are given in the following table.

Component	**Amount in formulation**	**Acetonitrile content**	**Daily exposure**
Active substance	0.3 g	800 ppm	0.24 mg
Excipient 1	0.9 g	400 ppm	0.36 mg
Excipient 2	3.8 g	800 ppm	3.04 mg
Veterinary medicinal product	5.0 g	728 ppm	3.64 mg

Excipient 1 meets the Option 1 limit, but the active substance, excipient 2, and the veterinary medicinal product do not meet the Option 1 limit. Nevertheless, the product meets the Option 2 limit of 4.1 mg per day and thus conforms to the recommendations in this guideline.

Consider another example using acetonitrile as residual solvent. The maximum administered daily mass of a veterinary medicinal product is 5.0 g, and the veterinary medicinal product contains two excipients. The composition of the veterinary medicinal product and the calculated maximum content of residual acetonitrile is given in the following table.

Component	**Amount in formulation**	**Acetonitrile content**	**Daily exposure**
Active substance	0.3 g	800 ppm	0.24 mg
Excipient 1	0.9 g	2000 ppm	1.80 mg
Excipient 2	3.8 g	800 ppm	3.04 mg
Veterinary medicinal product	5.0 g	1016 ppm	5.08 mg

In this example, the product meets neither the Option 1 nor the Option 2 limit. The manufacturer could test the product to determine if the formulation process reduced the level of acetonitrile. If the level of acetonitrile was not reduced during formulation to the allowed limit, then the manufacturer of the product should take other steps to reduce the amount of acetonitrile in the product or option 3 should be considered.

Option 3

Applicants may justify higher levels for the PDE and concentration limit based upon the actual daily dose, actual target species, and relevant toxicological data and considering consumer safety aspects. Use of Option 3 will be handled on a case by case basis by the regulatory authorities. This option may be applied as:

3a – The applicant may provide an appropriate body weight for the actual target species and / or the actual dose and recalculate the PDE and/or concentration limit using the ICH equations and ICH supporting toxicological data.

3b – The applicant may provide new toxicological data (with or without actual target animal and dose information) and recalculate the PDE and concentration limit using the equation provided by ICH.

If all of these steps fail to reduce the level of residual solvent, in exceptional cases the manufacturer could provide a summary of efforts made to reduce the solvent level to meet the guideline value, and provide a risk-benefit analysis to support allowing the product to be utilised with residual solvent at a higher level.

3.4 Analytical Procedures

Residual solvents are typically determined using chromatographic techniques such as gas chromatography. Any harmonised procedures for determining levels of residual solvents as described in the pharmacopoeias should be used, if feasible. Otherwise, manufacturers would be free to select the most appropriate validated analytical procedure for a particular application. If only Class 3 solvents are present, a non-specific method such as loss on drying may be used.
Validation of methods for residual solvents should conform to the VICH guidelines "Validation of analytical procedures: definition and terminology" and "Validation of analytical procedures: methodology."

3.5 Reporting Levels of Residual Solvents

Manufacturers of pharmaceutical products need certain information about the content of residual solvents in excipients or active substances in order to meet the criteria of this guideline. The following statements are given as acceptable examples of the information that could be provided from a supplier of excipients or active substances to a pharmaceutical manufacturer.

The supplier might choose one of the following as appropriate:

Only Class 3 solvents are likely to be present. Loss on drying is less than 0.5%.

Only Class 2 solvents X, Y, ... are likely to be present. All are below the Option 1 limit. (Here the supplier would name the Class 2 solvents represented by X, Y, ...)

Only Class 2 solvents X, Y, ... and Class 3 solvents are likely to be present. Residual Class 2 solvents are below the Option 1 limit and residual Class 3 solvents are below 0.5%.

If Class 1 solvents are likely to be present, they should be identified and quantified.

"Likely to be present" refers to the solvent used in the final manufacturing step and to solvents that are used in earlier manufacturing steps and not removed consistently by a validated process.

If solvents of Class 2 or Class 3 are present at greater than their Option 1 limits or 0.5%, respectively, they should be identified and quantified.

4. LIMITS OF RESIDUAL SOLVENTS

4.1 Solvents to be Avoided

Solvents in Class 1 should not be employed in the manufacture of active substances, excipients, and veterinary medicinal products because of their unacceptable toxicity or their deleterious environmental effect. However, if their use is unavoidable in order to produce a veterinary medicinal product with a significant therapeutic advance, then their levels should be restricted as shown in Table 1, unless otherwise justified. 1,1,1-Trichloroethane is included in Table 1 because it is an environmental hazard. The stated limit of 1500 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	1500	Environmental hazard

4.2 Solvents to be Limited

Solvents in 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
Cumene	0.7	70
Cyclohexane	38.8	3880
Cyclopentyl methyl ether	15.0	1500
1,2-Dichloroethene	18.7	1870
Dichloromethane	6.0	600
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
Methylisobutylketone	45	4500
N-Methylpyrrolidone	5.3	530
Nitromethane	0.5	50
Pyridine	2.0	200
Sulfolane	1.6	160
Tertiary-butyl alcohol	35	3500
Tetrahydrofuran	7.2	720
Tetralin	1.0	100
Toluene	8.9	890
1,1,2-Trichloroethene	0.8	80
Xylene*	21.7	2170

* usually 60% m-xylene, 14% p-xylene, 9% o-xylene with 17% ethyl benzene.

4.3 Solvents with Low Toxic Potential

Solvents in Class 3 (shown in Table 3) may be regarded as less toxic and of lower risk to target animal and human consumer 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 5000 ppm or 0.5% 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.

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
Dimethylsulfoxide	2-Methyltetrahydrofuran

Ethanol	Pentane
Ethyl acetate	1-Pentanol
Ethyl ether	1-Propanol
Ethyl formate	2-Propanol
Formic acid	Propyl acetate
	Triethylamine

4.4 Solvents For Which No Adequate Toxicological Data Was Found

The following solvents (Table 4) may also be of interest to manufacturers of excipients, active substances, or veterinary medicinal products. However, no adequate toxicological data on which to base a PDE was found. Manufacturers should supply justification for residual levels of these and other solvents for which a PDE has not been established for use in pharmaceutical products.

Table 4: Solvents for which no adequate Toxicological Data was found

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

GLOSSARY

Genotoxic carcinogens: Carcinogens which produce cancer by affecting genes or chromosomes.

LOEL: Abbreviation for lowest-observed effect level.

Lowest-observed effect level: The lowest dose of substance in a study or group of studies that produces biologically significant increases in frequency or severity of any effects in the exposed humans or animals.

Modifying factor: A factor determined by professional judgement of a toxicologist and applied to bioassay data to relate that data safely to humans.

Neurotoxicity: The ability of a substance to cause adverse effects on the nervous system.
NOEL: Abbreviation for no-observed-effect level.

No-observed-effect level: The highest dose of substance at which there are no biologically significant increases in frequency or severity of any effects in the exposed humans or animals.

PDE: Abbreviation for permitted daily exposure.

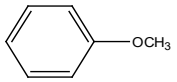
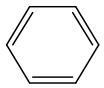
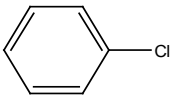
Permitted daily exposure: The maximum acceptable intake per day of residual solvent in pharmaceutical products.

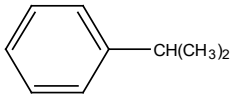
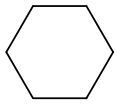
Reversible toxicity: The occurrence of harmful effects that are caused by a substance and which disappear after exposure to the substance ends.

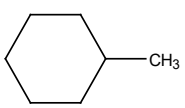
Strongly suspected human carcinogen: A substance for which there is no epidemiological evidence in humans of carcinogenesis but there are positive genotoxicity data and clear evidence of carcinogenesis in rodents (or other animal species).

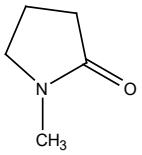
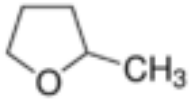
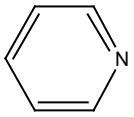
Teratogenicity: The occurrence of structural malformations in a developing fetus when a substance is administered during pregnancy.

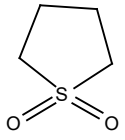
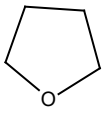
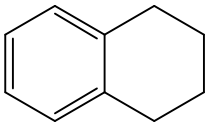
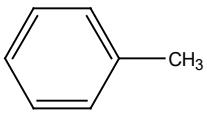
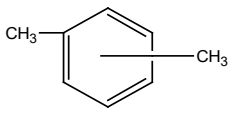
APPENDIX 1: LIST OF SOLVENTS INCLUDED IN THE GUIDELINE

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
Tertiary-butyl alcohol	t-Butyl alcohol *tert*-butanol	$(CH_3)_3COH$	Class 2
Carbon tetrachloride	Tetrachloromethane	CCl_4	Class 1
Chlorobenzene			Class 2
Chloroform	Trichloromethane	$CHCl_3$	Class 2

365 366	Cumene	Isopropylbenzene (1-Methyl)ethylbenzene		Class 2
367	Cyclohexane	Hexamethylene		Class 2
368 369	Cyclopentyl methyl ether	CPME		Class 2
370 371 372	1,2-Dichloroethane	*sym*-Dichloroethane Ethylene dichloride Ethylene chloride	CH_2ClCH_2Cl	Class 1
373 374	1,1-Dichloroethene	1,1-Dichloroethylene Vinylidene chloride	$H_2C=CCl_2$	Class 1
375 376	1,2-Dichloroethene	1,2-Dichloroethylene Acetylene dichloride	ClHC=CHCl	Class 2
377	Dichloromethane	Methylene chloride	CH_2Cl_2	Class 2
378 379 380	1,2-Dimethoxyethane	Ethyleneglycol dimethyl ether Monoglyme Dimethyl Cellosolve	$H_3COCH_2CH_2OCH_3$	Class 2
381	N,N-Dimethylacetamide	DMA	$CH_3CON(CH_3)_2$	Class 2
382	N,N-Dimethylformamide	DMF	$HCON(CH_3)_2$	Class 2
383 384 385	Dimethyl sulfoxide	Methylsulfinylmethane Methyl sulfoxide DMSO	$(CH_3)_2SO$	Class 3
386 387	1,4-Dioxane	p-Dioxane [1,4]Dioxane		Class 2
388	Ethanol	Ethyl alcohol	CH_3CH_2OH	Class 3

389	2-Ethoxyethanol	Cellosolve	$CH_3CH_2OCH_2CH_2OH$	Class 2
390	Ethyl acetate	Acetic acid ethyl ester	$CH_3COOCH_2CH_3$	Class 3
391	Ethyleneglycol	1,2-Dihydroxyethane	$HOCH_2CH_2OH$	Class 2
392		1,2-Ethanediol		
393	Ethyl ether	Diethyl ether	$CH_3CH_2OCH_2CH_3$	Class 3
394		Ethoxyethane		
395		1,1'-Oxybisethane		
396	Ethyl formate	Formic acid ethyl ester	$HCOOCH_2CH_3$	Class 3
397	Formamide	Methanamide	$HCONH_2$	Class 2
398	Formic acid		H C O O H	Class 3
399	Heptane	n-Heptane	$CH_3(CH_2)_5CH_3$	Class 3
400	Hexane	n-Hexane	$CH_3(CH_2)_4CH_3$	Class 2
401	Isobutyl acetate	Acetic acid isobutyl ester	$CH_3COOCH_2CH(CH_3)_2$	Class 3
402	Isopropyl acetate	Acetic acid isopropyl ester	$CH_3COOCH(CH_3)_2$	Class 3
403	Methanol	Methyl alcohol	CH_3OH	Class 2
404	2-Methoxyethanol	Methyl Cellosolve	$CH_3OCH_2CH_2OH$	Class 2
405	Methyl acetate	Acetic acid methyl ester	CH_3COOCH_3	Class 3
406	3-Methyl-1-butanol	Isoamyl alcohol	$(CH_3)_2CHCH_2CH_2OH$	Class 3
407		Isopentyl alcohol		
408		3-Methylbutan-1-ol		
409	Methylbutyl ketone	2-Hexanone	$CH_3(CH_2)_3COCH_3$	Class 2
410		Hexan-2-one		
411	Methylcyclohexane	Cyclohexylmethane		Class 2

412	Methylethyl ketone	2-Butanone	$CH_3CH_2COCH_3$	Class 3
413		MEK		
414		Butan-2-one		
415	Methylisobutyl ketone	4-Methylpentan-2-one	$CH_3COCH_2CH(CH_3)_2$	Class 2
416		4-Methyl-2-pentanone		
417		MIBK		
418	2-Methyl-1-propanol	Isobutyl alcohol	$(CH_3)_2CHCH_2OH$	Class 3
419		2-Methylpropan-1-ol		
420	N-Methylpyrrolidone	1-Methylpyrrolidin-2-one		Class 2
421		1-Methyl-2-pyrrolidinone		
422	2-Methyltetrahydrofuran	2-methyloxolane		Class 3
423		tetrahydrosylvan		
424	Nitromethane		CH_3NO_2	Class 2
425	Pentane	*n*-Pentane	$CH_3(CH_2)_3CH_3$	Class 3
426	1-Pentanol	Amyl alcohol	$CH_3(CH_2)_3CH_2OH$	Class 3
427		Pentan-1-ol		
428		Pentyl alcohol		
429	1-Propanol	Propan-1-ol	$CH_3CH_2CH_2OH$	Class 3
430		Propyl alcohol		
431	2-Propanol	Propan-2-ol	$(CH_3)_2CHOH$	Class 3
432		Isopropyl alcohol		
433	Propyl acetate	Acetic acid propyl ester	$CH_3COOCH_2CH_2CH_3$	Class 3
434	Pyridine			Class 2

435	Sulfonane	Tetrahydrothiophene 1,1-dioxide		Class 2
436 437	Tetrahydrofuran	Tetramethylene oxide Oxacyclopentane		Class 2
438	Tetralin	1,2,3,4-Tetrahydro-naphthalene		Class 2
439	Toluene	Methylbenzene		Class 2
440	1,1,1-Trichloroethane	Methylchlororoform	CH_3CCl_3	Class 1
441	1,1,2-Trichloroethene	Trichloroethene	$HClC=CCl_2$	Class 2
442	Triethylamine	N,N,-Diethylethanamine	$N(CH_2CH_3)_3$	Class 3
443 444	Xylene*	Dimethybenzene Xylol		Class 2

445

446 * usually 60 % m-xylene, 14 % p-xylene, 9 % o-xylene with 17 % ethyl benzene

447

APPENDIX 2: ADDITIONAL BACKGROUND

A2.1 Environmental Regulation of Organic Volatile Solvents

Several of the residual solvents frequently used in the production of pharmaceuticals are listed as toxic chemicals in Environmental Health Criteria (EHC) monographs and the Integrated Risk information System (IRIS). The objectives of such groups as the International Programme on Chemical Safety (IPCS), the United States Environmental Protection Agency (USEPA), and the United States Food and Drug Administration (USFDA) include the determination of acceptable exposure levels. The goal is protection of human health and maintenance of environmental integrity against the possible deleterious effects of chemicals resulting from long-term environmental exposure. The methods involved in the estimation of maximum safe exposure limits are usually based on long-term studies. When long-term study data are unavailable, shorter term study data can be used with modification of the approach such as use of larger safety factors. The approach described therein relates primarily to long-term or *life-time exposure of the general population* in the ambient environment, i.e. ambient air, food, drinking water and other media.

A2.2 Residual Solvents in Pharmaceuticals

Exposure limits in this guideline are established by referring to methodologies and toxicity data described in EHC and IRIS monographs. However, some specific assumptions about residual solvents to be used in the synthesis and formulation of pharmaceutical products should be taken into account in establishing exposure limits. They are:

Veterinary patients (rather than the general animal population) receive pharmaceuticals to treat their diseases or for prophylaxis to prevent infection or disease. However, there are some veterinary medicinal products which are used as aids in agricultural production which are unrelated to the presence of infection or disease in the animal population.

The assumption of life-time exposure of the veterinary patient is not necessary for most pharmaceutical products but may be appropriate as a working hypothesis to reduce risk to human health as a life-time exposure of the human consumer to the edible tissues of food animals treated with the veterinary medicinal product.

Residual solvents are unavoidable components in pharmaceutical production and will often be a part of veterinary medicinal products.

Residual solvents should not exceed recommended levels except in exceptional circumstances, and then should be justified.

Data from toxicological studies that are used to determine acceptable levels for residual solvents should have been generated using appropriate protocols including, but not necessarily limited to those described by OECD, EPA and the FDA Red Book.

APPENDIX 3: METHODS FOR ESTABLISHING EXPOSURE LIMITS

The Gaylor-Kodell method of risk assessment (Gaylor, D. W. and Kodell, R. L.: Linear Interpolation algorithm for low dose assessment of toxic substance. J Environ. Pathology, 4, 305, 1980) is appropriate for Class 1 carcinogenic solvents. Only in cases where reliable carcinogenicity data are available should extrapolation by the use of mathematical models be applied to setting exposure limits. Exposure limits for Class 1 solvents could be determined with the use of a large safety factor (i.e., 10,000 to 100,000) with respect to the no-observed-effect level (NOEL). Detection and quantitation of these solvents should be by state-of-the-art analytical techniques.

Acceptable exposure levels in this guideline for Class 2 solvents were established by calculation of PDE values according to the procedures for setting exposure limits in pharmaceuticals (Pharmacopeial Forum, Nov-Dec 1989), and the method adopted by IPCS for Assessing Human Health Risk of Chemicals (Environmental Health Criteria 170, WHO, 1994). These methods are similar to those used by the USEPA (IRIS) and the USFDA (Red Book) and others. The method is outlined here to give a better understanding of the origin of the PDE values. It is not necessary to perform these calculations in order to use the PDE values tabulated in Section 4 of this document.

PDE is derived from the no-observed-effect level (NOEL), or the lowest-observed effect level (LOEL) in the most relevant animal study as follows:

$$PDE = \frac{NOEL \times WeightAdjustmen}{F1 \times F2 \times F3 \times F4 \times F5}$$

The PDE is derived preferably from a NOEL. If no NOEL is obtained, the LOEL may be used. Modifying factors proposed here, for relating the data to humans, are the same kind of "uncertainty factors" used in Environmental Health Criteria (Environmental Health Criteria 170, World Health Organisation, Geneva, 1994), and "modifying factors" or "safety factors" in Pharmacopeial Forum. The assumption of 100% systemic exposure is used in all calculations regardless of route of administration.

The modifying factors are as follows:

F1 = A factor to account for extrapolation between species

F1 = 5 for extrapolation from rats to humans
F1 = 12 for extrapolation from mice to humans
F1 = 2 for extrapolation from dogs to humans
F1 = 2.5 for extrapolation from rabbits to humans
F1 = 3 for extrapolation from monkeys to humans
F1 = 10 for extrapolation from other animals to humans

F1 takes into account the comparative surface area: body weight ratios for the species concerned and for man. Surface area (S) is calculated as:

$$S = kM^{0.67}$$

in which M = body mass, and the constant k has been taken to be 10. The body weights used in the equation are those shown below in Table A3.1.

F2 = A factor of 10 to account for variability between individuals

A factor of 10 is generally given for all organic solvents, and 10 is used consistently in this guideline.

F3 = A variable factor to account for toxicity studies of short-term exposure
F3 = 1 for studies that last at least one half lifetime (1 year for rodents or rabbits; 7 years for cats, dogs and monkeys).
F3 = 1 for reproductive studies in which the whole period of organogenesis is covered.
F3 = 2 for a 6-month study in rodents, or a 3.5-year study in non-rodents.
F3 = 5 for a 3-month study in rodents, or a 2-year study in non-rodents.
F3 = 10 for studies of a shorter duration.

In all cases, the higher factor has been used for study durations between the time points, e.g. a factor of 2 for a 9-month rodent study.

F4 = A factor that may be applied in cases of severe toxicity, e.g. non-genotoxic carcinogenicity, neurotoxicity or teratogenicity. In studies of reproductive toxicity, the following factors are used:

F4 = 1 for fetal toxicity associated with maternal toxicity
F4 = 5 for fetal toxicity without maternal toxicity
F4 = 5 for a teratogenic effect with maternal toxicity
F4 = 10 for a teratogenic effect without maternal toxicity

F5 = A variable factor that may be applied if the no-effect level was not established
When only an LOEL is available, a factor of up to 10 could be used depending on the severity of the toxicity.

The weight adjustment assumes an arbitrary adult human body weight for either sex of 50 kg. This relatively low weight provides an additional safety factor against the standard weights of 60 kg or 70 kg that are often used in this type of calculation. It is recognised that some adult patients weigh less than 50 kg; these patients are considered to be accommodated by the built-in safety factors used to determine a PDE.

As an example of the application of this equation, consider a toxicity study of acetonitrile in mice that is summarised in Pharmeuropa, Vol. 9, No. 1, Supplement, April 1997, page S24. The NOEL is calculated to be 50.7 mg kg^{-1} day^{-1}. The PDE for acetonitrile in this study is calculated as follows:

$$PDE = \frac{50.7\,mg\,kg^{-1}day^{-1} \times 50\,kg}{12 \times 10 \times 5 \times 1 \times 1} = 4.22\,mg.day^{-1}$$

In this example,

F1 = 12 to account for the extrapolation from mice to humans
F2 = 10 to account for differences between individual humans
F3 = 5 because the duration of the study was only 13 weeks
F4 = 1 because no severe toxicity was encountered
F5 = 1 because the no effect level was determined

Table A.3.1: Values used in the calculations in this document

rat body weight	425g	mouse respiratory volume	43 L/day
pregnant rat body weight	330g	rabbit respiratory volume	1440 L/day
mouse body weight	28g	guinea pig respiratory volume	430 L/day
pregnant mouse body weight	30g	human respiratory volume	28,800L/day
guinea pig body weight	500g	dog respiratory volume	9,000 L/day
Rhesus monkey body weight	2.5kg	monkey respiratory volume	1,150 L/day
Rabbit body weight (pregnant or not)	4kg	mouse water consumption	5 mL
beagle dog body weight	11.5 kg	rat water consumption	30 mL/day
rat respiratory volume	290 L/day	rat food consumption	30 g/day

The equation for an ideal gas, PV = nRT, is used to convert concentrations of gases used in inhalation studies from units of ppm to units of mg/L or mg/m^3. Consider as an example the rat reproductive toxicity study by inhalation of carbon tetrachloride (molecular weight 153.84) is summarised in Pharmeuropa, Vol, 9, No. 1, Supplement, April 1997, page S9.

$$\frac{n}{V} = \frac{P}{RT} = \frac{300 \text{ x } 10^{-6} \text{ atm x } 153840 \text{ mg mol}^{-1}}{0.082 \text{ L atm K}^{-1} \text{ mol}^{-1} \text{ x } 298 \text{ K}} = \frac{46.15 \text{ mg}}{24.45 \text{L}} = 1.89 \text{ mg/L}$$

The relationship 1000 L = 1 m^3 is used to convert to mg/ m^3.