# Guidance for Industry

## Q3C Impurities: Residual Solvents

**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)**
**December 1997**
**ICH**

# Guidance for Industry

## Q3C Impurities: Residual Solvents

*Additional copies are available from:*
*Center for Drug Evaluation and Research (CDER),*
*Division of Drug Information (HFD-240),*
*5600 Fishers Lane, Rockville, MD 20857*
*(Tel) 301-827-4573*
*http://www.fda.gov/cder/guidance/index.htm*
*or*
*Office of Communication, Training, and*
*Manufacturers Assistance (HFM-40),*
*Center for Biologics Evaluation and Research (CBER)*
*1401 Rockville Pike, Rockville, MD 20852-1448,*
*http://www.fda.gov/cber/guidelines.htm;*
*(Fax) 888-CBERFAX or 301-827-3844*
*(Voice Information) 800-835-4709 or 301-827-1800*

**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)**
**December 1997**
**ICH**

## TABLE OF CONTENTS

# Guidance for Industry[1]

# Q3C Impurities: Residual Solvents

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

## I. INTRODUCTION (1)

The objective of this guidance is to recommend acceptable amounts for residual solvents in pharmaceuticals for the safety of the patient. The guidance recommends use of less toxic solvents and describes levels considered to be toxicologically acceptable for some residual solvents. A complete list of the solvents included in this guidance is provided in a companion document entitled *Q3C — Tables and List.*[2] The list is not exhaustive, and other solvents may be used and later added to the list.

Residual solvents in pharmaceuticals are defined here as organic volatile chemicals that are used or produced in the manufacture of drug substances or excipients, or in the preparation of drug products. The solvents are not completely removed by practical manufacturing techniques. Appropriate selection of the solvent for the synthesis of drug 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 guidance 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.

---

[1] This guidance was developed within the Expert Working Group (Quality) of the International Conference on Harmonisation of Technical Requirements for Registration of 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 bodies of the European Union, Japan, and the United States.

Arabic numbers in subsections reflect the organizational breakdown in the document endorsed by the ICH Steering Committee at Step 4 of the ICH process.

[2] This guidance was published originally in the *Federal Register* on December 24, 1997 (62 FR67377). At that time the list was included as Appendix 1. In this reformatted version, the list has been removed and made into a companion document, and the remaining appendices have been renumbered.

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. Drug 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, see Table 1 in the companion document *Q3C — Tables and List*) should be avoided in the production of drug substances, excipients, or drug products unless their use can be strongly justified in a risk-benefit assessment. Some solvents associated with less severe toxicity (Class 2, see Table 2 in the campanion document ) should be limited in order to protect patients from potential adverse effects. Ideally, less toxic solvents (Class 3, see Table 3 in the companion document) should be used where practical.

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 drug product containing a new solvent may be based on concepts in this guidance or the concept of qualification of impurities as expressed in the guidance for drug substance, *Q3A Impurities in New Drug Substances* (January 1996) or drug product, *Q3B Impurities in New Drug Products* (November 1997), or all three guidances.

## II. SCOPE OF THE GUIDANCE (2)

Residual solvents in drug substances, excipients, and drug products are within the scope of this guidance. 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 drug substances, excipients, or drug products. Although manufacturers may choose to test the drug product, a cumulative method may be used to calculate the residual solvent levels in the drug product from the levels in the ingredients used to produce the drug product. If the calculation results in a level equal to or below that recommended in this guidance, no testing of the drug product for residual solvents need be considered. If, however, the calculated level is above the recommended level, the drug product should be tested to ascertain whether the formulation process has reduced the relevant solvent level to within the acceptable amount. Drug product should also be tested if a solvent is used during its manufacture.

This guidance does not apply to potential new drug substances, excipients, or drug products used during the clinical research stages of development, nor does it apply to existing marketed drug products.

The guidance applies to all dosage forms and routes of administration. Higher levels of residual solvents may be acceptable in certain cases such as short-term (30 days or less) or topical application. Justification for these levels should be made on a case-by-case basis.

See Appendix 1 for additional background information related to residual solvents.

## III. GENERAL PRINCIPLES (3)

## A. Classification of Residual Solvents by Risk Assessment (3.1)

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

Residual solvents assessed in this guidance are listed in a companion document *entitled Q3C — Tables and List*. Common names and structures are used. 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—

> Nongenotoxic 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 PDE's of 50 milligrams (mg) or more per day.

## B. Methods for Establishing Exposure Limits (3.2)

The method used to establish permitted daily exposures for residual solvents is presented in Appendix 2. Summaries of the toxicity data that were used to establish limits are published in *Pharmeuropa,* Vol. 9, No. 1, Supplement, April 1997.

## C. Options for Describing Limits of Class 2 Solvents (3.3)

Two options are available when setting limits for Class 2 solvents.

*Option 1*: The concentration limits in parts per million (ppm) stated in Table 2 (see companion document) can be used. They were calculated using equation (1) below by assuming a product mass of 10 mass of 10 grams (g) mass of 10 grams administered daily.

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

Here, PDE is given in terms of mg/day and dose is given in g/day.

These limits are considered acceptable for all substances, excipients, or products. Therefore, this option may be applied if the daily dose is not known or fixed. If all excipients and drug 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 each component of the drug product to comply with the limits given in Option 1. The PDE in terms of mg/day as stated in Table 2 (see companion document) can be used with the known maximum daily dose and equation (1) above to determine the concentration of residual solvent allowed in drug 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, and 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 drug 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 drug 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 drug product is 5.0 g, and the drug product contains two excipients. The composition of the drug product and the calculated maximum content of residual acetonitrile are given in the following table.

| **Component** | **Amount in Formulation** | **Acetonitrile Content** | **Daily Exposure** |
|---|---|---|---|
| Drug 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 |
| Drug product | 5.0 g | 728 ppm | 3.64 mg |

*Excipient 1* meets the Option 1 limit, but the drug substance, excipient 2, and drug 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 guidance.

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

| Component | Amount in Formulation | Acetonitrile Content | Daily Exposure |
|---|---|---|---|
| Drug substance | 0.3 g | 800 ppm | 0.24 mg |
| Excipient 1 | 0.9 g | 2,000 ppm | 1.80 mg |
| Excipient 2 | 3.8 g | 800 ppm | 3.04 mg |
| Drug Product | 5.0 g | 1,016 ppm | 5.08 mg |

In this example, the product meets neither the Option 1 nor the Option 2 limit according to this summation. The manufacturer could test the drug 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 drug product should take other steps to reduce the amount of acetonitrile in the drug product. 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 guidance value, and provide a risk-benefit analysis to support allowing the product to be utilized with residual solvent at a higher level.

## D. Analytical Procedures (3.4)

Residual solvents are typically determined using chromatographic techniques such as gas chromatography. Any harmonized 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 nonspecific method such as loss on drying may be used.

Validation of methods for residual solvents should conform to ICH guidances, *Q2A Text on Validation of Analytical Procedures* (March 1995) and *Q2B Validation of Analytical Procedures: Methodology* (November 1996).

## E. Reporting Levels of Residual Solvents (3.5)

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

- 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 percent.

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 percent, respectively, they should be identified and quantified.

## IV. LIMITS OF RESIDUAL SOLVENTS (4)

### A. Solvents to Be Avoided (4.1)

Solvents in Class 1 (Table 1; see companion document) 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 (see companion document) because it is an environmental hazard. The stated limit of 1,500 ppm is based on a review of the safety data.

### B. Solvents to Be Limited (4.2)

Solvents in Class 2 (Table 2; see companion document) 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.

### C. Solvents with Low Toxic Potential (4.3)

Solvents in Class 3 (Table 3; see companion document) 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).

## D. Solvents for Which No Adequate Toxicological Data Were Found (4.4)

The solvents listed in Table 4 (see companion document) 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.

## GLOSSARY

**Genotoxic carcinogens**: Carcinogens that 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 judgment 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 of carcinogenesis but there are positive genotoxicity data and clear evidence of carcinogenesis in rodents.

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

## APPENDIX 1: ADDITIONAL BACKGROUND

### Environmental Regulation of Organic Volatile Solvents (A2.1)

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 U.S. Environmental Protection Agency (EPA), and the U.S. Food and Drug Administration (FDA) 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 *lifetime exposure of the general population* in the ambient environment (i.e., ambient air, food, drinking water, and other media).

### Residual Solvents in Pharmaceuticals (A2.2)

Exposure limits in this guidance 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 as follows:

- Patients (not the general population) use pharmaceuticals to treat their diseases or for prophylaxis to prevent infection or disease.

- The assumption of lifetime patient exposure is not necessary for most pharmaceutical products but may be appropriate as a working hypothesis to reduce risk to human health.

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

- Residual solvents should not exceed recommended levels except in exceptional circumstances.

- Data from toxicological studies that are used to determine acceptable levels for residual solvents should have been generated using appropriate protocols such as those described, for example, by the Organization for Economic Cooperation and Development, EPA, and the FDA Red Book.

## APPENDIX 2: METHODS FOR ESTABLISHING EXPOSURE LIMITS

The Gaylor-Kodell method of risk assessment (Gaylor, D. W., and R. L. Kodell, "Linear Interpolation Algorithm for Low Dose Assessment of Toxic Substance," *Journal of Environmental Pathology and Toxicology*, 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 NOEL. Detection and quantitation of these solvents should be by state-of-the-art analytical techniques.

Acceptable exposure levels in this guidance 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 (EHC 170, WHO, 1994). These methods are similar to those used by the U.S. EPA (IRIS) and the U.S. FDA (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 NOEL or the LOEL in the most relevant animal study as follows:

$$PDE = \frac{\text{NOEL} \times \text{Weight Adjustment}}{F1 \times F2 \times F3 \times F4 \times F5} \qquad (1)$$

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 EHC (EHC 170, WHO, Geneva, 1994), and *modifying factors* or *safety factors* in *Pharmacopeial Forum*. The assumption of 100 percent 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:

$$S = kM^{0.67} \quad (2)$$

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 guidance.

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 nonrodents.

F3 = 5 for a 3-month study in rodents, or a 2-year study in nonrodents.

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., nongenotoxic 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 NOEL 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 kilograms (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 recognized 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. If the solvent was present in a formulation specifically intended for pediatric use, an adjustment for a lower body weight would be appropriate.

As an example of the application of this equation, consider a toxicity study of acetonitrile in mice that is summarized 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:

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

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 NOEL was determined.

**Table A3.1 – Values Used in the Calculations in This Document**

| | | | |
|---|---|---|---|
| Rat body weight | 425 g | Mouse respiratory volume | 43 liter (L)/day |
| Pregnant rat body weight | 330 g | Rabbit respiratory volume | 1,440 L/day |
| Mouse body weight | 28 g | Guinea pig respiratory volume | 430 L/day |
| Pregnant mouse body weight | 30 g | Human respiratory volume | 28,800 L/day |
| Guinea pig body weight | 500 g | Dog respiratory volume | 9,000 L/day |
| Rhesus monkey body weight | 2.5 kg | Monkey respiratory volume | 1,150 L/day |
| Rabbit body weight (pregnant or not) | 4 kg | Mouse water consumption | 5 milliliter (mL)/day |
| 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/cubic meter ($m^3$). Consider as an example the rat reproductive toxicity study by inhalation of carbon tetrachloride (molecular weight 153.84) summarized in *Pharmeuropa*, Vol. 9, No. 1, Supplement, April 1997, page S9.

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

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