1.11

ICH Q3C Guideline

Impurities: Residual Solvents

Comments for its Application

1. Introduction

Residual solvents defined as organic volatile chemicals

- Used or produced in the synthesis of drug substances or excipients,
- Used in preparation of drug product.

Guideline does not address solvents deliberately used as excipients nor does it address solvates

No higher levels of residual solvents than can be supported by safety data.

2. Scope of the Guideline

Testing should be performed when production or
Purification process are known to result in 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,
- Drug product.

A cumulative method may be used to calculate the residual solvents from the levels in the ingredients used for the product.

If the calculation results in levels below that recommended in this guideline no testing need to be considered.

If the calculation level is above the recommended level, drug product should be tested, possible reduction through formulation process.

3. General Principles

3.1 Classification of Residual solvents by Risk Assessment.

Definitions:

TDI: Tolerable Daily Intake
PDE: Permitted Daily Exposure

Residual solvents are listed in the Appendix I and placed in one of the three classes:

- **Class 1 solvents: Solvents to be avoided**

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

- **Class 2 solvents: Solvents to be limited**

- **Class 3 solvents: Solvents with low toxic potential**

  No health based expose limit is needed. They have PDEs of 50 mg or more per day

3.2 Options for describing limits for class 2 solvents

Option 1:

The concentration limits in ppm in Table 2 can be used.
They were calculated using the following equation by assuming a product mass of 10 g administered daily
This option is used if daily dose is not yet known

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

PDE in mg/day, dose in g/day

Example Acetonitrile

PDE: 4.1 mg/day

$\frac{1000 \times 4.1}{10}$ = 410 ppm Option 1 limit: 410 ppm

No further calculation is necessary provided the daily dose does not exceed 10 g.

If daily dose in greater than 10 g option 2 should be considered.

3.3 Options for describing limits for class 2 solvents

Option 2

It is applied by adding the amounts of a residual solvent present in each of the components of the product. The sum of the amounts of solvents per day should be less than that given by PDE.

The maximum daily administered mass is 5 g. The composition of the drug product contains two excipients. The data are given in the table

Component	Amount in formulation	Acetonitrile Content	Equation	Daily exposure
Drug substance	0.3 g	800 ppm	$\frac{800 \times 0.3}{1000}$	0.24 mg
Excipient 1	0.9 g	400 ppm	$\frac{400 \times 0.9}{1000}$	0.36 mg
Excipient 2	3.8 g	800 ppm	$\frac{800 \times 3.8}{1000}$	3.04 mg
Drug product	5.0 g	728 ppm	$\frac{800 \times 3.8}{1000}$	3.64

Drug product meets option 2 limit as PDE 4.1 mg/day

3.4 Analytical procedures

Chromatographic techniques such as gas chromatography

If only class 3 solvents are present, a nonspecific method such as loss on drying may be used.

3.5 Reporting levels of residual Solvents

❒ **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%.