

ORGANIC VOLATILE **IMPURITIES AND THEIR REGULATORY** **LIMITS** **(AS A PART OF PREFORMULATION)**

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(1) INTRODUCTION

Impurities in pharmaceuticals are the unwanted chemicals that remain with active pharmaceutical ingredients (APIs), or develop during formulation, or upon aging of APIs and formulated APIs to medicines.

Webster's dictionary defines impurity as something that is impure or makes something else impure. Presence of these unwanted impurities may influence the efficacy & safety of pharmaceutical products.

But sometimes the presence of some impurities may not deleteriously impact on drug quality if therapeutic efficacy is similar to or greater than the drug substance itself. Nevertheless, a drug substance can be considered as compromised with respect to purity even if it contains an impurity with superior pharmacological or toxicological properties.

So identification & isolation of impurities are more important. It is identified & isolated by using the following analytical methods-

- Mass spectroscopy

- Fourier transform ion cyclotron resonance mass spectroscopy (FT-ICR-MS)

- Nuclear magnetic resonance (NMR)

- High performance liquid chromatography (HPLC)

Also different pharmacopoeias, such as the British pharmacopoeia (BP), United States pharmacopoeia (USP), are slowly incorporating limits to allowable levels of impurities present in the APIs or formulation. The International Conference on Harmonization (ICH) has published guidelines on impurities in new drug substances.

(2) TYPES OF IMPURITY

Two types of impurities in medicines-

- (a) impurities associated with APIs &

- (b) impurities that form are created during formulation & or with aging or that are related to formulated forms.

According to ICH guidelines, impurities associated with APIs are classified into the following categories-

- (a) Organic impurities

- (b) Inorganic impurities

- (c) Residual solvents

- (d) Other materials

(a) Organic impurities

- Starting materials

- Process related impurities

- Intermediates

- Degradation products

(b) Inorganic impurities

- Salts

- Catalysts

Ligands
Heavy metals

(c) Residual solvents

(d) Other materials

Filter aids
Charcoal

According to United State Pharmacopoeias(USP)

- (a) Impurities in official articles
- (b) Ordinary impurities
- (c) Organic volatile impurities

Also the following terms have used by the USP to describe impurities-

▶ **Foreign substances**

The materials that are introduced by contamination or adulteration, not as a consequence of synthesis or preparation, are labeled foreign subs..
e.g., pesticides in oral analgesic.

▶ **Toxic impurities**

These impurities have significant undesirable biological activity.

▶ **Concomitant components**

Bulk pharmaceuticals chemicals may contain concomitant components.
e.g. Antibiotics that are mixtures and are geometric and optical isomer.

▶ **Signal impurities**

These impurities include some process-related impurities or degradation products that provide key information about the process.

▶ **Ordinary impurities**

The species of impurities in bulk pharmaceutical chemicals that are innocuous by virtue of having no significant undesirable biological activity in the amounts present are called ordinary impurities.

▶ **Organic volatile impurities**

OVI are generally solvents used in the synthesis or during the formulation of the drug product.

(3) SOURCES OF IMPURITIES

▶ **Starting materials**

These are the materials that are used to begin the synthesis of an APIs.e.g. paracetamol bulk, there is a limit test for p-amino phenol, which could starting materials for some one manufactures or be intermediate for others.

▶ **Intermediates**

The compounds during synthesis of the desired materials are called intermediates.

▶ **Penultimate intermediate(Final intermediates)**

As the name suggests ,this is the last compound in the synthesis chain prior to the production of the desired compound.

▶ **By-products**

The unplanned compound produced in the reaction are generally called by- products. e.g. In paracetamol bulk diacetylated paracetamol may form as a By-products.

▶ **Interaction products**

This is a slightly more comprehensive term than the two described above(by-products and transformation products);however ,it is more difficult to evaluate in that it considers interactions that could occur between various chemicals-intentionally or unintentionally.Two types of interaction products that can be commonly encountered are drug substance-excipient interactions and drug substance –container /closer interactions.

▶ **Related products**

This term tends to suggest that the impurity is similar to the drug substance. e.g. Hydrates in Isoniazide which produce hepatotoxicity.

▶ **Degradation products**

These are the compound produced because of decomposition of material of interest or APIs.

e.g. The degradation of penicillins and cephalosporins is well known example.The presence of β -lactam ring as well as that of an amino group in the C6/C7 chain plays critical role in there degradation.

Q3C(R3)

Impurities: Guideline for Residual Solvents

Q3C

**Impurities: Guideline for Residual Solvents (Maintenance)
PDE for Tetrahydrofuran (in Q3C(R3))**

Q3C(M)

Recommended for Adoption at Step 4 of the ICH Process on 17 July 1997 by the ICH Steering Committee. Birth of ICH at **April 1990**.

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA

(4.1) INTRODUCTION

The objective of this guideline is to recommend acceptable amounts for residual solvents in pharmaceuticals for the safety of the patient.

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 or remains after 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 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.

(4.2) SCOPE OF THE GUIDELINE

Residual solvents in drug substances, excipients, and in drug products are within the scope of this guideline. Therefore, testing should be performed for residual solvents when production or purification processes. It is only necessary to test for solvents that are used or produced in the manufacture or purification of drug substances, excipients, or drug product.

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 guideline, 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 guideline 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 guideline 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.

(4.3) GENERAL PRINCIPLES

(4.3.1) 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 Organization (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 ADI's 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.

e.g., Benzene, Carbon tetrachloride, 1,1-Dichlorobenzene, etc

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.

e.g., Acetonitrile, Chlorobenzene, Chloroform, Cyclohexane, 1,4-Dioxane, etc.

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.

e.g., Acetone, Anisole, 1-Butanol, Cumene, Ethyl ether, etc.

Class 4 solvents: Solvents for which no toxicological data have been found

Solvents for which no adequate toxicological data have been found.

e.g., 1,1-Dichloroethane, Trifluoroacetic acid, Ethyl acetate, etc.

(4.3.2) Methods for Establishing Exposure Limits:-

The Gaylor-Kodell method of risk assessment, 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. 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:

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

The PDE is derived preferably from a NOEL.

If no NOEL is obtained, the LOEL may be used.

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.

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 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.

(4.3.3)Options for Describing Limits of Class 2 Solvents:-

Two 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 given below by assuming a product mass of 10 g administered daily.

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

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 necessary for each component of the drug product to comply with the limits given in Option 1. 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 (gm)	Acetonitrile content (ppm)	Daily exposure (mg)
Drug substance	0.3	800	0.24
Excipient 1	0.9	400	0.36
Excipient 2	3.8	800	3.04
Drug product	5.0	728	3.64

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 guideline.

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 is given in the following table.

Component	Amount in formulation (gm)	Acetonitrile content (ppm)	Daily exposure (mg)
Drug substance	0.3	800	0.24
Excipient 1	0.9	2000	1.80
Excipient 2	3.8	800	3.04
Drug product	5.0	1016	5.08

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 guideline value, and provide a risk benefit analysis to support allowing the product to be utilised with residual solvent at a higher level.

(4.3.4) Analytical Procedures:-

Residual solvents are typically determined using chromatographic techniques such as gas chromatography. Other methods are LC-MS, HPLC, Mass Spectroscopy. 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 nonspecific method such as loss on drying may be used.

Solvents are used frequently to dissolve film-coating material to facilitate application onto compressed tablets. These tablets are subjected to air drying to remove all organic solvents from coat of finished product. The residual levels of these organic solvents in tablet core and film coats are critical, because they cause undesirable side effects.

Determination of Methylene chloride organic volatile impurity in marketed formulations of Ciprofloxacin, Norfloxacin, Pefloxacin, and Ofloxacin:

The most sensitive among the methods for monitoring the amount of residual solvents in the marketed solid dosage formulations is the Gas chromatographic method.

First, the Standard Analytical Grade is taken and diluted with particular solvent for ex. Methylene chloride as impurity solvent diluted with dimethyl sulfoxide. The retention time is recorded in Gas chromatogram.

Then, tablets which are coated or formulated with this solvent are taken and crushed and extracted with diluting solvent. So whatever methylene chloride present that will extract out and that filtered. Retention time of this filtrate taken. As per retention time of standard methylene chloride, peak intensity or area, amount of test methylene calculated.

(4.3.5) Reporting levels of residual solvents:-

Quantitative results should be presented numerically, and not in general terms such as “complies” or “meets limits”.

Below 1.0 %, the results should be reported to two decimal places (e.g. 0.06%, 0.31%);at and above 1%, the results should be reported to one decimal place (e.g. 1.3%).

Impurities should be designated by code number or by an appropriate descriptor e.g. retention time

(4.4) LIMITS OF RESIDUAL SOLVENTS:-

(4.4.1) Solvents to Be Avoided:-

Solvents in Class 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. 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.

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

(4.4.2) Solvents to Be Limited:-

Solvents in given table 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	3880
1,2-Dichloroethene	18.7	1870
Dichloromethane	6.0	600
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	6.2	620
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
N-Methylpyrrolidone	48.4	4840
Nitromethane	0.5	50
Pyridine	2.0	200
Sulfolane	1.6	160
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.

(4.4.3) Solvents with Low Toxic Potential:-

Solvents in Class 3 (*shown in Table 3*) may be regarded as less toxic and of lower risk to human health. Class 3 includes no solvent known as a human health hazard at levels normally accepted in pharmaceuticals.

However, there 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, 1-Butanol, 3-Methyl-1-butanol, tert-Butylmethyl ether, 2-Methyl-1-propanol, Ethanol, 1-Propanol, Ethyl formate, Tetrahydrofuran	Anisole, Methyl acetate, Butyl acetate, Methylisobutyl ketone, Dimethylsulfoxide, 1-Pentanol, Ethyl ether, Propyl acetate	Isopropyl acetate, 2-Butanol, Methylethyl ketone, Cumene, Pentane, Ethyl acetate, 2-Propanol, Formic acid,

(4.4.4) Solvents for which No Adequate Toxicological Data was Found

The following solvents (*Table 4*) may also be of interest to manufacturers of excipients, drug substances, or drug products. However, no adequate toxicological data on which to base a PDE was found. Manufacturers should supply justification for residual levels of these solvents in pharmaceutical products.

Table 4. Solvents for which no adequate toxicological data was found are given below.

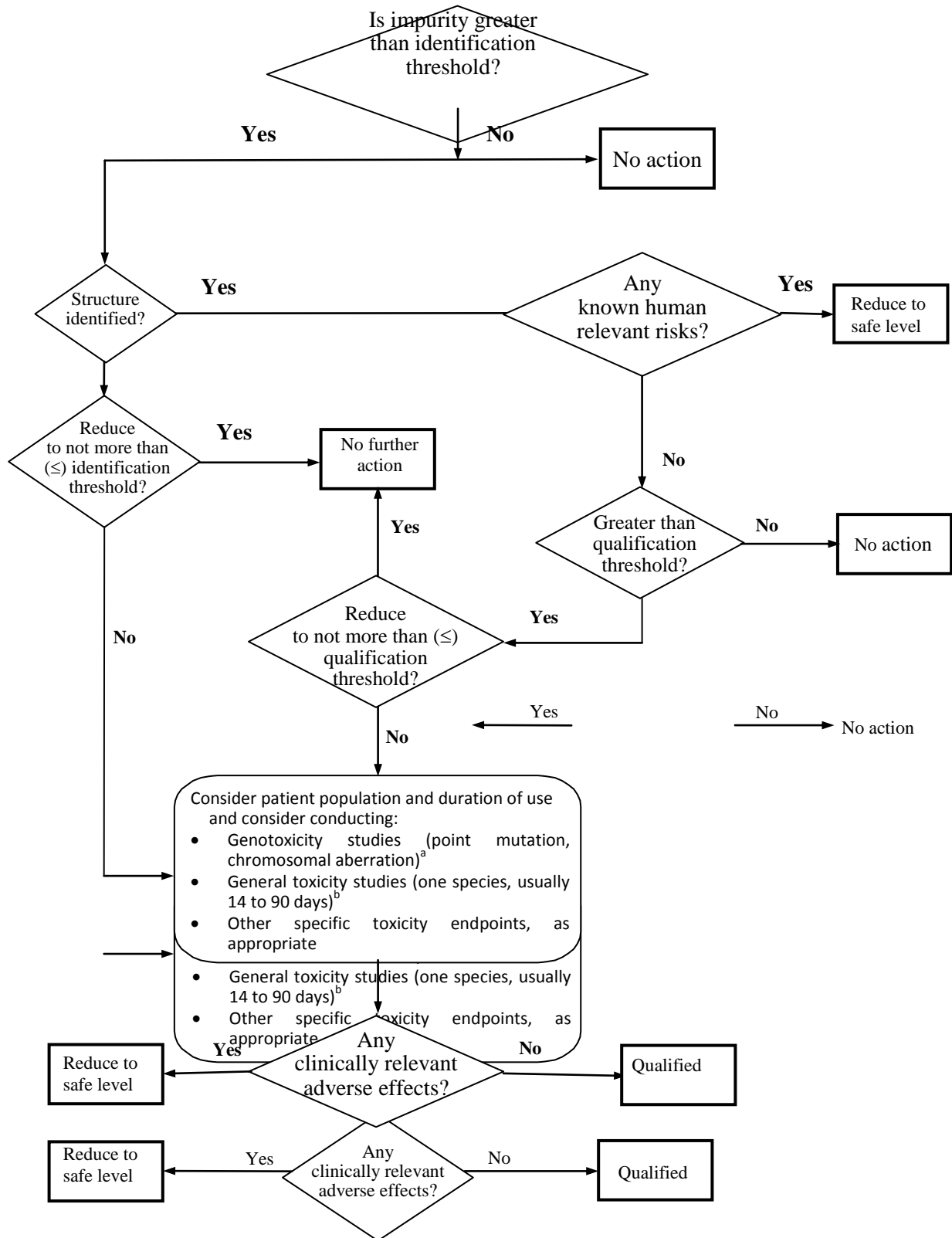
1,1-Diethoxypropane, Methyltetrahydrofuran Isooctane, acid	Methylisopropyl ketone, 2,2-Dimethoxypropane, Trichloroacetic acid,	1,1-Dimethoxymethane, Petroleum ether, Isopropyl ether Trifluoroacetic
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(5)As per U.S. Pharmacopoeia regulatory limits

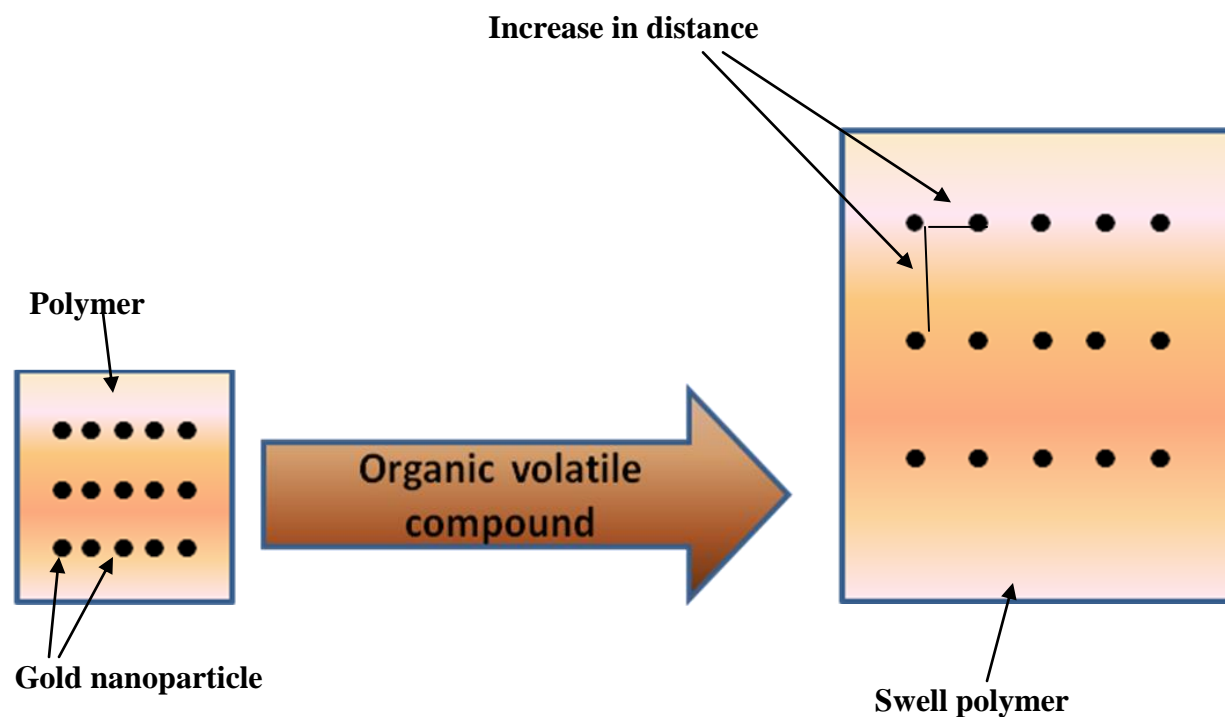
Organic volatile impurities	USP/NF limits before 2003 (ppm)	USP/NF 2003 limits (ppm)
Benzene	100	Not specific
Chloroform	50	60
1,4-Dioxane	100	380

Methylene chloride	500	600
Trichloroethylene	100	80

FIGURE2: DECISION TREE FOR IDENTIFICATION AND QUALIFICATION



Polymer-metal nanocomposites with two dimensional gold nanoparticle for sensoric application of organic volatile compounds



Questions:

- (1) Classify impurities present in APIs? Sept-2004
- (2) How will you calculate PDE in OVIs? Apr-2005
- (3) OVIs Sept-2006
- (4) Classify impurities and how they are addressed in new drug substance? Apr-2006

Study Questions:

- What are impurities? Write a note on sources of impurities
- What are residual solvents? Why we take care in selection of appropriate solvents?
- What is PDE? Classify residual solvents by risk assessment.
- How will you calculate PDE of class-1 and class-2 solvents?
- Describe a limits of residual solvents
- Draw a decision tree for identification & qualification

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