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USP Chemical Test ⟨467⟩: Residual Solvents

What are Residual Solvents?

Residual solvents, previously known as Organic Volatile Impurities (OVIs), are chemicals that are not completely removed from the manufacture or preparation of pharmaceutical drug substances, excipients, or products. Residual solvents should be removed or limited as much as possible since they do not provide any therapeutic benefit and may be carcinogenic, toxic, or environmentally hazardous. In the evaluation of possible health risks, residual solvents have been categorized into three classes, assessed by different levels of toxicity.

Class	Assessment
1	• To be avoided • Known or strongly suspected to be carcinogenic • Environmental hazards
2	• To be limited • Possible causes of irreversible toxicity • Suspected of reversible toxicities
3	• Have low toxic potential • No health-based exposure limit needed • PDE limit is 50mg per day

How do we test for them?

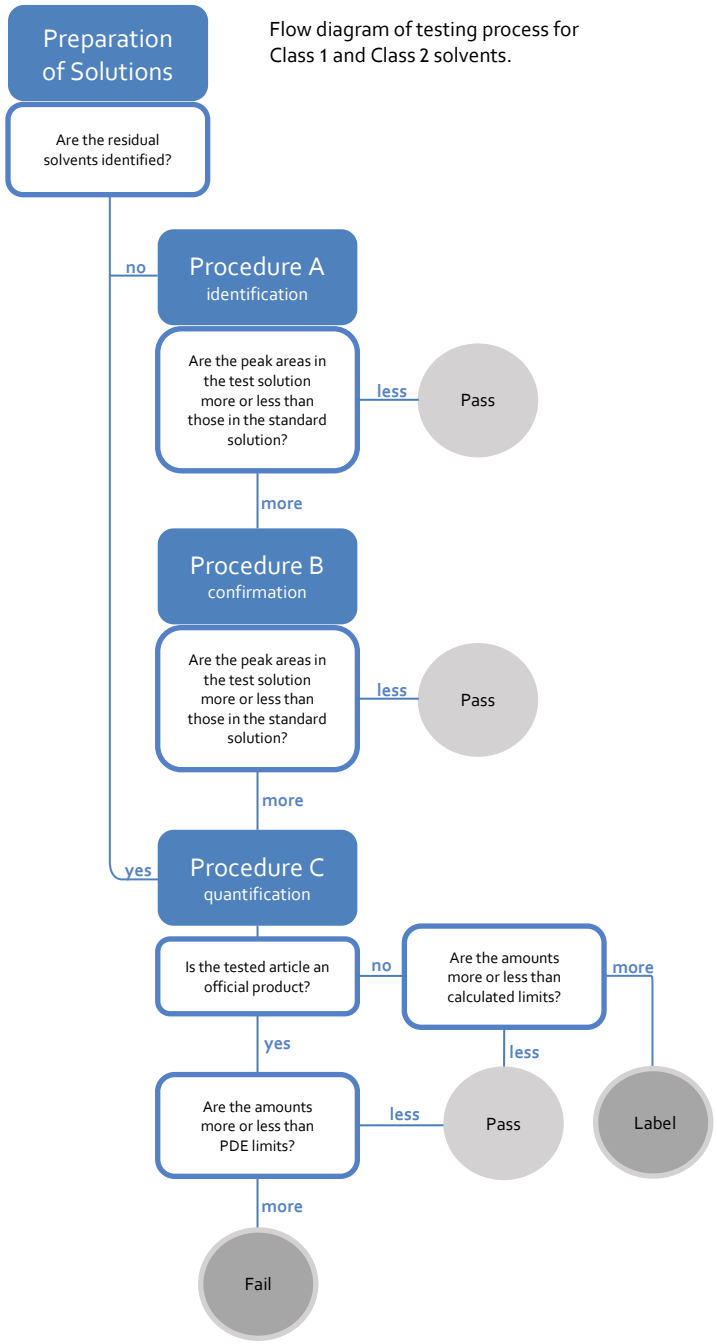
The analytical technique of gas chromatography separates compounds in samples, resulting in peaks that show at different times corresponding to a particular compound. The data is compared between the test solution and standard solutions (USP Reference Standards), which contain the upper concentration limits of a mix of solvents. Class 1 and Class 2 solvents are identified and quantified using the process on the right. Class 3 solvents are quantified using USP ⟨761⟩, the Loss On Drying method.

Why do we test for them?

The United States Pharmacopoeia (USP) contains Permitted Daily Exposure (PDE) limits of common residual solvents. The purpose of USP Method ⟨467⟩ is to identify and quantify residual solvents that are likely to be present. The results would determine whether the amount of residual solvents in the tested sample complies with the limits defined in the USP, which is required by the FDA of all existing commercial drug products.

Using this method, drug manufacturers have the option to test either the final drug product or drug components. We can also test on drug excipients, raw materials, or items for veterinary use.

At EuTech Scientific Services, we are committed to providing unambiguous, reliable, and accurate results to meet your needs in analytical testing. We adhere to GLP guidelines of the FDA. All work is performed in our state-of-the-art facilities under strict confidentiality.



Flow diagram of testing process for Class 1 and Class 2 solvents.

EuTech Scientific Services
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31 May 2017

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Residual Solvent Limits

CLASS 1

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

CLASS 2

	solvent	PDE (mg/day)
Mixture A	acetonitrile	4.1
	chlorobenzene	3.6
	cumene	0.7
	cyclohexane	38.8
	1,2-dichloroethene	18.7
	1,4-dioxane	3.8
	methanol	30.0
	methylcyclohexane	11.8
	methylene chloride	6.0
	tetrahydrofuran	7.2
	toluene	8.9
	xylene*	21.7
Mixture B	chloroform	0.6
	1,2-dimethoxyethane	1.0
	hexane	2.9
	methylbutylketone	0.5
	nitromethane	0.5
	pyridine	2.0
	tetralin	1.0
	trichloroethylene	0.8
Mixture C	N,N-dimethylaceamide	10.9
	N,N-dimethylformamide	8.8
	2-ethoxyethanol	1.6
	ethylene glycol	6.2
	formamide	2.2
	2-methoxyethanol	0.5
	sulfolane	1.6
	N-methylpyrrolidone	5.3

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

CLASS 3

solvent
acetic acid
acetone
anisole
1-butanol
2-butanol
butyl acetate
tert-butylmethyl ether
dimethyl sulfoxide
ethanol
ethyl acetate
ethyl ether
ethyl formate
formic acid
heptane
isobutyl acetate
isopropyl acetate
methyl acetate
3-methyl-1-butanol
methylethylketone
methylisobutylketone
2-methyl-1-propanol
pentane
1-pentanol
1-propanol
2-propanol
propyl acetate
PDE limit: 50 mg/day

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