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Impurities are guidelines for residual solvents

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Residual solvents in pharmaceuticals are defined as organic volatile chemicals that are used as vehicles or produced in the manufacture of drug substances or excipients, or in the preparation of drug products. The solvents used in the manufacturing process have a great impact on the physical characteristics of a drug substance such as polymorphic form, crystal shape, purity and solubility.

Since these residual solvents do not offer any therapeutic benefits for the patients, and sometimes they are potentially toxic, all these residual solvents should be removed to the extent possible to meet Drug product specification, good manufacturing practices, or other quality-based requirements.

Moreover, the Drug products should not contain residual solvents at higher level than can be supported by safety data ICH Guideline (ICH Q3C) is intended to provide recommendations on acceptable amounts for residual solvents in pharmaceuticals for the safety of the patient. The guideline also recommends use of less toxic solvents and describes levels considered to be toxicologically acceptable for some residual solvents.

This guideline is applicable to Drug Substances, Excipients and all dosage forms and routes of administration but does not apply to potential new drug substances, excipients, or drug products used during the clinical research stages of development as well as existing marketed drug products. The parent guideline (ICH Q3C) has been revised periodically to include PDE of Tetrahydrofuran (THF), N-methylpyrrolidone (NMP), Cumene, Triethylamine (TEA) and Methyisobutylketone (MIBK) based on their new toxicological data. The current valid version is ICH Q3C (R6).

As the solvents used in the process or produced during the manufacturing process are not removed completely by practical manufacturing techniques, hence, selection of a solvent to be used in the process is very critical. Depending upon the toxicity, the solvents have been classified into three categories:

Class 1 Solvents (Solvents to be avoided):

Class 1 solvents are known human carcinogens, strongly suspected human carcinogens and environmental hazards, and their use should be avoided in the manufacture of drug substances, excipients, or drug products unless their use can be strongly justified in a risk-benefit assessment.

Class 2 Solvents (Solvents to be limited):

Class 2 solvents are non-genotoxic animal carcinogens or possible causative agents of other irreversible toxicity such as neurotoxicity or teratogenicity. In order to protect patients from potential adverse effects, use of Class 2 solvents should be limited.

Class 3 Solvents (Solvents with low potential toxic):

Class 3 solvents having low toxic potential to man, should be used where practical. Hence, no health-based exposure limit is needed. Class 3 solvents have PDEs of 50 mg or more per day. Higher amounts may also be acceptable provided they are realistic in relation to manufacturing capability and good manufacturing practice (GMP).

If Class 3 solvents adversely affect quality attributes such as stability when present at levels consistent with ICH Q3C, it may be appropriate to set the acceptance criteria for those solvents below ICH Q3C levels to reduce or prevent the adverse effect.

Methods for establishing exposure limits (Class 1 and Class 2 Solvents):

The permitted Daily Exposure (PDE) for residual solvents (Class 1 and Class 2 are established based on their toxicity data. The method used to establish permitted daily exposures for residual solvents is presented in Appendix 3 of ICH Guidelines for residual solvents ICH Q3C.

Class 1 Solvent:

Permitted Daily Exposure limits for Class 1 solvents were 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.

Class 2 Solvents:

Acceptable exposure levels for Class 2 solvents were established by calculation of PDE values derived from the no-observed-effect level (NOEL), or the lowest-observed effect level (LOEL) in the most relevant animal study. The assumption of 100% systemic exposure is used in all calculations regardless of route of administration.

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