

Regulation of Residual Solvents in Medicinal Products in the European Union
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The EU adopted the ICH guideline on residual solvents into its regulatory process in 1997 following the completion of the Step 4 of the ICH guideline (Q3C), together with the additional changes through the maintenance programme. Given that the basis for the controls applied and the acceptance criteria defined was rooted in safety concerns, it was considered illogical to apply this only to new products containing new active substances as is the general aim of ICH guidance. Therefore, the European Medicines Agency and its Quality Working Party took the decision to extend the provisions within a two-year timeframe to all new applications containing new and established active substances as well as to products already on the market so that the same residual solvent controls would apply to all medicinal products in Europe.

In parallel, the European Pharmacopoeia, which is the official Pharmacopoeia named in the European Union, decided to adopt the ICH criteria for controlling residual solvents into its General Chapters and monographs. Notwithstanding that the European Pharmacopoeia is an institution of the Council of Europe and has a wider audience than the twenty-five Member States of the European Union, there was unanimous agreement amongst the Member States signatories to the European Pharmacopoeia Convention that ICH based residual solvent control limits were appropriate for all medicinal products covered by the European Pharmacopoeia. Consequently, a General Chapter was developed which implemented the ICH Q3C residual solvent guideline verbatim and a reference was made in the general monograph on Substances for Pharmaceutical Use to apply the residual solvent standards to all substances, active and excipients, described in the European Pharmacopoeia. Furthermore, in 2005 it has been agreed that acceptance criteria for Class II solvents would not be mentioned in the European Pharmacopoeia monographs and that Class I solvents would be included only where it was known that their use was unavoidable in the manufacturing process for the drug substance using the acceptance criteria laid down in the ICH guidelines.

Finally, it is also recognised that some specific substances produce solvated forms for which there are frequently higher levels of solvents, for example, Class III solvents co-crystallising with the active substances for which higher limits than the normal general 0.5% limit may have to be applied. These higher-level Class III solvents would then be named individually on a case-by-case basis where their presence at such levels is considered to be unavoidable. It should be stressed that there is no safety issue relating to such levels since they are low toxicity solvents and the 0.5% threshold is merely a nominal limit. It should also be stressed that this does not bind the regulatory authorities in the European Union to adopt wider limits than the ICH limits of such low toxicity solvents if they feel the need from a safety point of view in insisting that a higher limit in line with the ICH guidance is more appropriate for a given source of an active substance.