

Residual Solvents--ICH Perspective
Robert E. Osterberg, R.Ph., Ph.D.
Aclairo Pharmaceutical Development Group

In December of 1977, the Residual Solvent guidance, Q3C, reached step 5. This allowed the three ICH regulatory authorities (US, EU, JP) to publish this "Quality" guidance for use in their respective drug developing regions. It was recognized that the PDE or Permissible Daily Exposure value for each solvent could be changed when and if more reliable animal toxicity data was reviewed by the Expert Working Group (EWG). Two years later, the issue of guideline maintenance was formally agreed upon and a Maintenance EWG was formed.

It was the function of the Q3C EWG to develop a list of residual pharmaceutical solvents and provide explanations for their placement in the 4 toxicity categories (Solvents: to be avoided; to be limited; with low toxic potential; for which no adequate toxicological data were found) that were developed by this EWG. The EWG contained several chemists from each of the 3 ICH regions, one toxicologist from each 6-pack member plus observers from non-ICH member regions such as Canada and China.

The 59 residual solvents identified were assigned to one category based upon the severity and types of their toxicities. Ten other solvents were identified but insufficient toxicity data placed them in the fourth toxicity category.

When the Maintenance EWG was formed, within a year it changed the PDEs for two of the residual solvents, N-Methylpyrrolidone and Tetrahydrofuran because of the acquisition of new and more reliable toxicity data.

A discussion regarding the development of the guideline and its maintenance will be presented.