INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

IMPURITIES : RESIDUAL SOLVENTS (MAINTENANCE) PDE FOR TETRAHYDROFURAN Q3C(M)

Recommended for Adoption

at Step 4 of the ICH Process

on 12 September 2002

by the ICH Steering Committee

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.

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PDE FOR TETRAHYDROFURAN

ICH Harmonised Tripartite Guideline

Having reached *Step 4* of the ICH Process at the ICH Steering Committee meeting on 12 September, 2002, this guideline is recommended for adoption to the three regulatory parties to ICH

The ICH Q3C guidance reached step 5 in December of 1997. It had been agreed by the members of the Expert Working Group (EWG) that the permissible daily exposure (PDE) could be modified if reliable and more relevant toxicity data was brought to the attention of the group. In 1999, a maintenance agreement was instituted and a Maintenance EWG was formed. The agreement provided for the re-visitation of solvent PDEs and allowed for minor changes to the guidance that included the existing PDEs. It was also agreed that new solvents and PDEs could be added based upon adequate toxicity data.

The EWG visited new toxicity data for the solvent tetrahydrofuran (THF) late last year and earlier this year. The data in review was the information published by the U. S. National Toxicology Program (NTP) that consisted of data from several mutagenicity studies and two carcinogenicity studies in rodents via the inhalational route of administration. Information was sent to the members of the EWG for their analysis.

Animal Toxicity

Genetic toxicology studies were conducted in Salmonella typhimurium, Chinese hamster ovary cells, Drosophila melanogaster, mouse bone marrow cells and mouse peripheral blood cells. The *in vitro* studies were conducted with and without exogenous metabolic activation from induced S9 liver enzymes. With the exception of an equivocal small increase above baseline in male mouse erythrocytes, no positive findings were found in any of the genetic toxicology studies.

Groups of 50 male and 50 female rats were exposed to 0, 200, 600, or 1,800 ppm tetrahydrofuran by inhalation, 6 hours per day, 5 days per week, for 105 weeks. Identical exposures were given to groups of 50 male and 50 female mice. Under the conditions of the studies, there was some evidence of carcinogenic activity of THF in male rats due to increased incidences of adenoma or carcinoma (combined) of the kidney. There was clear evidence of carcinogenic activity of THF in female mice due to increased incidences of hepatocellular adenomas and carcinomas. No evidence for carcinogenicity was found in female rats and male mice.

Using the lowest THF exposure in the most sensitive specie, the male rat at 200 ppm was used for the PDE calculation.

$$200\ \text{ppm} = \frac{200 \text{ x } 72.10}{24.45} = 589.8\ \text{mg/m}^3 = 0.59\ \text{mg/L}$$

$$\text{For continuous dosing} = \frac{0.59 \text{ x } 6 \text{ x } 5}{24 \text{ x } 7} = 0.105\ \text{mg/L}$$

$$\text{Daily dose} = \frac{0.105 \text{ x } 290}{0.425} = 71.65\ \text{mg/kg}$$

$$\text{PDE} = \frac{71.65 \text{ x } 50}{5 \text{ x } 10 \text{ x } 1 \text{ x } 10 \text{ x } 1} = 7.165\ \text{mg/day} = \mathbf{7.2\ mg/day}$$

$$\text{Limit} = \frac{7.2 \text{ x } 1000}{10} = \mathbf{720\ ppm}$$

Conclusion:

The former PDE for this solvent was greater than 50 mg/day (121 mg/day) and THF was placed in Class 3. The newly calculated PDE for tetrahydrofuran based upon chronic toxicity/carcinogenicity data is 7.2 mg/day, therefore, **it is recommended that Tetrahydrofuran be placed into Class 2** in Table 2 in the ICH Impurities: Residual Solvents Guideline. This is also the appropriate Class for THF because this Class contains those solvents that are non-genotoxic carcinogens and THF has been demonstrated to be a non-genotoxic carcinogen in rodents.