

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

ICH HARMONISED TRIPARTITE GUIDELINE

**IMPURITIES : RESIDUAL SOLVENTS (MAINTENANCE)
PDE FOR N-METHYLPYRROLIDONE (NMP)
Q3C(M)**

Recommended for Adoption
at Step 4 of the ICH Process
on 12 September 2002
by the ICH Steering Committee

*(Two mistyping corrections in the first calculation formula have been given
on October 28, 2002 – this version is corrected)*

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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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 received new toxicity data for the solvent N-methylpyrrolidone late last year. It had been provided to the FDA by the NMP Producers Group. It was a 2-year chronic feeding study in rats performed by E.I. Dupont de Nemours & Co (unpublished data). The data was sent to the members of the EWG for their analysis. At the time, that data appeared to be the best available upon which to make a recommendation to the Steering Committee regarding a change in the status of NMP. At the last ICH meeting, February 28 to March 2, 2000, I briefed the Steering Committee on the results of the EWG's analysis and its consensus decision. The consensus was to remove NMP from Class 2 (PDE of 48.4 mg/day) and place it into Class 3 with a new PDE of 207 mg/day. Shortly thereafter, members of the EWG provided additional comment and data from which lower PDEs could be determined. The following paragraphs contain an analysis of an appropriate and more sensitive study from which to calculate a new PDE.

Animal Toxicity

The following paper was used for the calculation of the PDE for NMP:

“Effects Of Prenatal Exposure To N-Methylpyrrolidone On Postnatal Development And Behaviour In Rats”, Hass U. et al., Neurotoxicol. Teratol.: 1994, 16, (3), 241-249.

Wistar rats were exposed by inhalation to 150ppm NMP for 6 hours/day, daily from days 7-20 of gestation and were then allowed to litter. No maternal toxicity was detected and litter size was unaffected by treatment. No physical abnormalities were described. The offspring were reduced in weight, the difference being statistically significant up to week 5 after birth. Pre-weaning development was impaired as was higher cognitive function related to solving of difficult tasks. Basal function of the CNS was normal and there were no effects on learning of low

grade tasks. A NOEL was not established.

$$150 \text{ ppm} = \frac{150 \times 99.13}{24.45} = 608.16 \text{ mg/m}^3 = 0.608 \text{ mg/L}$$

$$\text{For continuous dosing} = \frac{0.608 \times 6}{24} = 0.152 \text{ mg/L}$$

$$\text{Daily dose} = \frac{0.152 \times 290}{0.33} = 133.58 \text{ mg/kg}$$

$$\text{PDE} = \frac{133.58 \times 50}{5 \times 10 \times 1 \times 5 \times 5} = \mathbf{5.3 \text{ mg/day}}$$

$$\text{Limit} = \frac{5.3 \times 1000}{10} = \mathbf{530 \text{ ppm}}$$

Conclusion:

This study was chosen because of the toxicity endpoint that was seen, that is, the effect of the solvent on the function of the developing nervous system in utero. This is a potentially serious toxicity since we do not know if it is a permanent effect or if it is reversible. We are not sure if this delayed development could be due to the lower body weight of the pups. However, the EWG has decided to be cautious in its interpretation and in its safety decision.

The EWG members thus recommend that **N-methylpyrrolidone should be kept in Class 2** in Table 2 in the ICH Impurities: Residual Solvents Guideline. A new PDE and limit as described above should also be declared for this solvent. Class 2 contains those solvents that have significant toxicities such as neurotoxicity, non-genotoxic carcinogenicity, teratogenicity etc., and should be limited in their use up to the PDE limits listed in the table.