Impurities: Residual Solvents
ICH: Q3C

Robert E. Osterberg, R.Ph., Ph.D., Fellow-ATS
Aclairo Pharmaceutical Development Group
Vienna, Virginia

USP 1/2007
ICH and Residual Solvents

1- Purpose and History of the ICH:
   a) Beginning
   b) Organisation
   c) Expert Working Groups (EWGs)

2- Q3C Guidance Document
   a) Organisation, data used, assumptions made
   b) Classes of solvents and examples
   c) Maintenance
What is the ICH?

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
Purpose of the ICH

**Purpose** - to make recommendations on ways:

- to achieve greater harmonisation in the interpretation, application of technical guidelines and presentation of documentation
- to reduce or obviate the need to duplicate testing in R&D of new medicines
- to make better economical use of human, animal and material resources
- to eliminate delay in drug development
- to maintain safeguards on quality, safety and efficacy and regulatory obligations to protect public health.
History of ICH

- Birth of ICH-April 1990 in Brussels
- 1st meeting in Brussels in 1991
- Meetings often in Brussels, Washington, Tokyo and other cities
- Involves the EU, Japan and the USA
- There are 6 co-sponsors:
  JPMA, MHLW, EC, EFPIA, PhRMA
  and the FDA (IFPMA provides the Secretariat) -2 members each to Steering Committee
- Invited observers-Canada, China, WHO, EFTA, 3 Pharmacopeias, generic drug association representatives and others
ICH Topics

Five main subject areas:
1- Quality
2- Safety
3- Efficacy
4- Multidisciplinary
5- Regulatory Communications
Q3C Impurities: Residual Solvents

Guidance objective-to recommend acceptable amounts for residual solvents in pharmaceuticals for the safety of the patient

Residual Solvents = organic volatile chemicals used or produced in the making of drug substances or excipients or in the preparation of drug products.
Q3C continued

The guidance:
- recommends use of less toxic solvents
- gives toxicologically acceptable levels of some solvents
- does not address all possible solvents, only those identified in drugs at that time
- does not address solvents deliberately used as excipients nor solvates.
Q3C continued

- There is no therapeutic benefit from residual solvents so,

- Drug products should contain no higher levels than can be supported by safety data. *

- Use of Class 1 solvents (most toxic) should be avoided unless strongly justified.

- Class 2 solvents should be limited to protect patients from potential toxicities.

- Class 3 solvents (least toxic) should be used where practical.

  * and be patient acceptable
The guidance:

- does **not** apply to potential new drug substances, new excipients or drug products used during clinical stages of drug development, nor to existing marketed drug products.

- applies to **all** dosage forms and routes of administration.

- but higher levels may be acceptable in certain cases such as short-term use (<31 days) or for topical drug administration.
Class 1 solvents: Substances to be avoided i.e., known human carcinogens, strongly suspected human (genotoxic) carcinogens and environmental hazards. 

Examples: concentration limit

- benzene 2 ppm
- carbon tetrachloride 4 ppm
- 1,2-dichloroethane 5 ppm
- 1,1-dichloroethene 8 ppm
- 1,1,1-trichloroethane 1,500 ppm
**Q3C continued**

*Class 2 solvents*: Substances to be limited, i.e., non-genotoxic carcinogens, teratogens, genotoxicants, solvents that can cause severe but **reversible** CNS, liver, kidney, etc. toxicities.

**Examples**:  

<table>
<thead>
<tr>
<th>Substance</th>
<th>Concentration Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>cyclohexane</td>
<td>3880 ppm</td>
</tr>
<tr>
<td>dichloromethane</td>
<td>600 ppm</td>
</tr>
<tr>
<td>NMP</td>
<td>530 ppm (4,840 ppm)</td>
</tr>
<tr>
<td>pyridine</td>
<td>200 ppm</td>
</tr>
<tr>
<td>toluene</td>
<td>890 ppm</td>
</tr>
<tr>
<td>xylene</td>
<td>2170 ppm</td>
</tr>
<tr>
<td>tetrahydrofuran</td>
<td>720 ppm (12,100 ppm)</td>
</tr>
</tbody>
</table>
Class 3 solvents: Substances with low toxic potential. Amounts should not exceed 50 mg/day or 5,000 ppm or 0.5%

**Examples:**

- acetone
- ethanol
- DMSO
- heptane
- isopropyl acetate
- methylethyl ketone
- butyl acetate
- ethyl acetate
- 1-pentanol
- ethyl ether
- tetrahydrofuran*
Class 4 solvents: Substances for which no adequate toxicological data were found. (a PDE can not be determined)

**Examples:**

- isopropyl ether
- 1.1-dimethoxymethane
- methylisopropyl ketone
- isooctane
- petroleum ether
- trichloroacetic acid
PDE Calculation for Class 2 Solvents

NOEL x Human Body Weight

PDE = -------------------------------------------------------------

F1 x F2 x F3 x F4 x F5

F1 = extrapolation between species
F2 = variability among individuals
F3 = study duration
F4 = severity of toxicity
F5 = used if NOEL not established
Exposure Limits

Limits for Class 2 solvents:

Option 1:
Concentration (ppm) = $1000 \times \frac{\text{PDE}}{\text{dose}}$
- dose = 10g/d of solvent

Option 2: add the amounts of a residual solvent present in each of the components of the drug product. The sum should be < PDE.
Q3C Maintenance EWG

Instituted in 1999 and a regulatory rapporteur was selected.

PDE could be modified if reliable and more relevant toxicity data was obtained.

In June 2000, 2 reports were received by the EWG, NMP and THF.

**Actions:**

- NMP- PDE from 48.4 to 207 to 5.3 mg/d
- THF- PDE from 121 to 7.2 mg/d
- EG- PDE of 6.2 mg/d for **long** term use;
- 40 mg/d for **short** term use
Thank You