ICH Q3C(R8) – Residual Solvent

Step 2 document – to be released for comments

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International Council for Harmonisation of Technical Requirements
for Pharmaceuticals for Human Use

Legal Notice

Background – Q3C Maintenance

- The ICH Q3C core guideline reached *Step 4* in 1997.
- In 1999 a maintenance agreement was instituted and a Maintenance Expert Working Group (EWG) was formed.
- The agreement provided for the re-visitation of solvent Permitted Daily Exposure (PDE) and allowed for minor changes to the guideline that included the existing PDEs.
- It was also agreed that new solvents and PDEs could be added based upon adequate toxicity data.

Background

- This 8th revision (R8) of the document has been signed off as a *Step 2* document (25 March 2020) to be issued by the ICH Regulatory Members for public consultation
- The document was originally developed based on a Concept Paper (10 March 1994)
- Anticipating finalization as a *Step 4* document to be implemented in the local regional regulatory system: July 2020

Guideline Objectives

- **The objectives of the current Maintenance procedure are to add three new solvents to the guideline:**
  - 2-Methyltetrahydrofuran
  - Cyclopentyl Methyl Ether
  - Tertiary Butyl Alcohol

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2-Methyltetrahydrofuran (2-MTHF)

- EWG's review of available toxicity data with 2-MTHF
  - Genotoxicity: no evidence for genotoxicity
  - Carcinogenicity: no data available
  - Reproductive toxicity: no reliable studies for PDE calculation
  - Repeat dose toxicity: two rat sub-chronic oral studies; No-observed-effect-level (NOEL) considered appropriate for PDE calculation

2-MTHF: PDE calculation*

*see Q3C guideline for details of PDE calculation

- Rat sub-chronic (3-month) oral studies
  - Effects at 500 mg/kg/day or greater included changes in kidney weight, cholesterol, prothrombin time, and hepatocellular hypertrophy
  - NOEL of 250 mg/kg/day used for PDE
  - PDE = 50 mg/day
  - Since the PDE is greater than or equal to 50 mg/day, 2-MTHF is placed into Class 3 ("solvents with low toxic potential")

Cyclopentyl methyl ether (CPME)

- EWG's review of available toxicity data with CPME
  - Genotoxicity: no evidence for genotoxicity
  - Carcinogenicity: no data available
  - Reproductive toxicity: a 2-generation study in rats demonstrated decreased body weights of pups; however, detailed information from study is not available.
  - Repeat dose toxicity: two rat sub-chronic oral studies and one rat sub-chronic inhalation study; No-observed-effect-level (NOEL) from rat 28-day oral study considered most appropriate for PDE calculation.

CPME: PDE calculation*

*see Q3C guideline for details of PDE calculation

- Rat sub-chronic (28-day) oral study
  - Effects at 700 mg/kg/day (high dose) included lethality, salivation, increased respiration, and CNS effects.
  - NOEL of 150 mg/kg/day (mid dose) used for PDE
  - PDE = 15 mg/day
  - Since CPME is associated with significant toxicities and a PDE of 15 mg/day, CPME is placed into Class 2 ("solvents to be limited")

Tertiary butyl alcohol (TBA) - 1

- EWG's review of available toxicity data with TBA
  - Genotoxicity: no evidence for genotoxicity
  - Reproductive toxicity: limited data available.
    - Some evidence of induced developmental delays and mortality at relatively high oral doses.
    - Additional reports of reduced mean litter size, number of live born pups and pup body weight, and increased pup mortality and number of stillborn pups.

Tertiary butyl alcohol (TBA) - 2

- EWG's review of available toxicity data with TBA
  - Repeat dose toxicity: two sub-chronic oral (drinking water) studies in rats and mice
    - In rats:
      - Lethality observed at highest dose (2824 mg/kg/day)
      - Other key findings included nephropathy and hyperplasia/inflammation of the urinary bladder.
      - Lowest-observed-effect-level (LOEL) of 176 mg/kg/day identified due to increased incidence of nephropathy.
    - In mice:
      - Lethality observed at highest dose (7143 mg/kg/day)
      - Other key findings included reduced body weight and hyperplasia/inflammation of the urinary bladder at the two highest doses
      - NOEL of 1786 mg/kg/day was identified.

Tertiary butyl alcohol (TBA) - 3

- EWG's review of available toxicity data with TBA
  - Carcinogenicity:
    - TBA was studied in 2-year rat and mouse drinking water studies
    - Primary targets of TBA toxicity and carcinogenicity were the kidney in rats, and thyroid gland and urinary bladder in mice
    - NTP's conclusion: "some evidence of carcinogenic activity" in male rats and female mice
  - The 2-year carcinogenicity studies were considered the most appropriate to support calculation of the PDE
    - Individual PDEs were calculated for each study (see following slides)

TBA: PDE calculation* - 1

*see Q3C guideline for details of PDE calculation

- Rat 2-year study:
  - Renal lesions and tumour findings in male rats are not relevant to humans
  - Increased severity in nephropathy observed in female rats at all doses used for PDE calculation (LOEL = 175 mg/kg/day)
  - PDE = 35 mg/day

TBA: PDE calculation* - 2

*see Q3C guideline for details of PDE calculation

- Mouse 2-year study:
  - Thyroid adenomas increased in high dose females
  - Increased incidence and severity of thyroid follicular hyperplasia in TBA-treated groups used for PDE calculation (LOEL = 510 mg/kg/day)
  - Increased incidence of urinary bladder inflammation and hyperplasia of transitional epithelium at high dose
  - PDE = 42.5 mg/day

TBA: PDE calculation* - 3

*see Q3C guideline for details of PDE calculation

- The overall PDE was identified as 35 mg/day
- Since TBA is associated with significant toxicities and a PDE of 35 mg/day, TBA is placed into Class 2 (“solvents to be limited”)

Conclusions

- **A Q3C Maintenance procedure has been initiated to add 3 new solvents: 2-MTHF, CPME, and TBA**
- **The proposed PDEs are as follows:**
  - 2-MTHF: 50 mg/day (Class 3)
  - CPME: 15 mg/day (Class 2)
  - TBA: 35 mg/day (Class 2)

Contact

- **For any questions please contact the ICH Secretariat:**

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