ICH M7 Guideline on Mutagenic Impurities

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• The information within this presentation is based on the presenter's expertise and experience, and represents the views of the presenter for the purposes of a training workshop.
Basis for addressing mutagenic impurities

• Drug synthetic processes involve the use of reactive starting materials, intermediates and reagents
  o Some are known or potential genotoxicants, carcinogens
  o Reaction coupling to generate active pharmaceutical ingredient (API)

• Low levels of mutagenic impurities may appear in the final drug substance or product

• How do we manage risk and quality, both during drug development and post-registration?
ICH M7 Guideline on Mutagenic Impurities

History

2000-2004
- ICH Q3A/B (R) issued in 2002
  - “Lower thresholds may be appropriate for unusually toxic impurities”
  - Lacks specific guidance on how to address mutagenic/carcinogenic impurities
- Increased awareness and regulatory scrutiny on residual levels of genotoxic impurities in API and drug products
- EMEA issues draft guidance, stressing avoidance vs. acceptance of a low limit

2004
- EMEA updates draft guidance and introduces the TTC limit (1.5 ug/day) for drugs

2005
- PhRMA Publication (Müller et al., 2006). “A rationale for determining, testing and controlling specific impurities in pharmaceuticals that possess potential for genotoxicity”
  - Introduces concept of the ‘staged TTC’ for clinical trial materials
History (continued)

2007

- CHMP Q&A document generated based on industry questions and EMA answers

2008

- EMA letter requesting evaluation of sulfonate esters in all marketed products

2009-10

- November 2009 – Concept paper issued and ICH M7 topic agreed
- September 2010 – CHMP Q&A document updated
- November 2010 – First ICH EWG M7 Meeting in Fukuoka Japan
Threshold of Toxicological Concern (TTC) concept as a basis for characterizing risk

- Pragmatic approach for establishing an exposure threshold for all chemicals below which there is no appreciable risk to human health (e.g. cancer)
  - For drugs, TTC limit established at 1.5 ug/day (1 in 100,000 cancer risk) (CHMP)

- For carcinogenicity, it is based on the more potent carcinogens
  - Carcinogenic potencies range over 100 million fold.
  - Many genotoxic carcinogens are lower potency, so "risk" level much lower than 1 in $10^5$

- Linear extrapolation from rodent carcinogenic dose
  - Most sensitive sex, species and site of tumors
  - No allowance for threshold

- Lifetime exposure assumed (70 years)
  - Most drugs are not given for a lifetime
  - Staged TTC: Considers less than lifetime exposures (e.g. clinical development)
ICH M7 Topic for Harmonization

- Deliverable (M7 Business Plan): Harmonized guideline for evaluation and control of mutagenic impurities
  - What are acceptable limits during development and marketing?
  - Regulated using threshold of toxicological concern (TTC) approach?
  - Treating multiple impurities?
  - Addressing impurities that are metabolites
  - Situations and data to support exceptions for higher acceptable daily intakes than the TTC?
## M7 Expert Working Group (EWG)

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Invited RHI/DRA/DoH representatives: Mr. Zhang Wei and Dr. Chen Zhen, DRA China
• Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk
  o Objective was to place focus on limiting carcinogenic risk of low level DNA-reactive mutagenic impurities
Issues for M7 Guideline Development

• Refine considerations and elements for conducting assessments
  o From clinical development to post-marketing scenarios
  o Retrospective application of the guideline (e.g. process route changes)

• Use of predictive *in silico* tools to identify structures of concern to base further assessments on
  o Assessment elements, process, what and how many tools to use?

• Application of TTC concepts and consideration of alternative risk approaches to limit carcinogenic risk

• Defining important elements in a control strategy of mutagenic impurities
  o From the use of process understanding and ‘quality by design’ principles to end product testing
ICH M7 EWG Progress and Status

• **General timelines**
  o Targeting Step 1 first draft June 2011
  o Target date for Step 2 document Nov 2012

• **Step 1 starting working draft developed Dec 2010**

• **Some members attended and presented at the April 2011 DIA QSAR Workshop – *in silico* approaches**

• **Elluminate *Live!* meetings held (May 2011) to prioritize key topic areas where data/information and further discussions are needed to reach an agreed position**

• **EWG Meeting (Cincinnati) (June 13-16)**
  o Assemble case examples and alternative position proposals to present, review and discuss. Establish agreed positions. (Day 1)
  o Revise/construct remaining Step 1 draft sections towards completion of 1st draft (Days 2-4)