



ICH M7 Guideline on Mutagenic Impurities

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Disclaimer:

- **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**
 - Some are known or potential genotoxicants, carcinogens
 - 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?**

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- EMEA issues draft guidance, stressing avoidance vs. acceptance of a low limit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- EMEA updates draft guidance and introduces the TTC limit (1.5 ug/day) for drugs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 Guideline on the Limits of Genotoxic Impurities effective January 2007.
- CHMP Q&A document generated based on industry questions and EMA answers

2008

- FDA Draft Guidance for Industry. Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches.
- 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)

Party	Topic Leader	Deputy Topic Leader	Expert	Observer	Interested Party
EU	Peter Kasper	Diana van Riet-Nales			
EFPIA	Steven Spanhaak	Lutz Muller	Kevin McKiernan		
MHLW	Masamitsu Honma	Yukio Aso	Mari Yoshitomi		
JPMA	Shigeki Sawada	Tomonori Konse	Kazusei Komatsu		
FDA	David Jacobson-Kram	Stephen Miller	Aisar Atrakchi		
PhRMA	Warren Ku	David De Antonis	Joseph DeGeorge		
EFTA				Elisabeth Klenke	
HC				Alisa Vespa	
WSMI					Esther Vock
IGPA					Jack Lipman
DRA of China			Sun Tao		
DRA of Singapore			Looi Yee Hoo		

Invited RHI/DRA/DoH representatives: Mr. Zhang Wei and Dr. Chen Zhen, DRA China

Draft ICH M7 Guideline Title

- Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk
 - 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**
 - From clinical development to post-marketing scenarios
 - 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**
 - 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**
 - From the use of process understanding and ‘quality by design’ principles to end product testing

ICH M7 EWG Progress and Status

- **General timelines**
 - Targeting Step 1 first draft June 2011
 - 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)**
 - Assemble case examples and alternative position proposals to present, review and discuss. Establish agreed positions. (Day 1)
 - Revise/construct remaining Step 1 draft sections towards completion of 1st draft (Days 2-4)



Thank You!