ICH M7 (R2) – Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk Questions and Answers

Step 2 document – to be released for comments

29 June 2020

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

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Outline

- Background
- Q&As Objectives and Work process
- Q&As
- Conclusions

Background

- The ICH M7 guideline was adopted by ICH in June 2014 and the first addendum (R1) was adopted in May 2017
- This Q&A document was developed to provide additional clarification to details having led to differing interpretation by stakeholders
- A Concept Paper (Sep 19th 2018) has been developed to guide the development of the Q&A
- The Q&A has been signed off as a *Step 2* document by the Assembly (*Step 2a*) and the Regulatory Members of the Assembly (*Step 2b*) in May 2020 to be issued by the ICH Regulatory Members for public consultation
- The EWG anticipates to finalize as a *Step 4* document November / 2020

Q&A Objectives

- **Clarification of details in the guideline document which led to different interpretation by stakeholders**
  - Justification of control strategy in marketing authorization applications
  - Organization and detail of information on mutagenic impurities in marketing authorization applications
  - (Q)SAR systems
- **Promote further harmonization in using this guidance in regulation of mutagenic impurities in pharmaceuticals**

Q&A Work process

- **Stakeholders submitted more than 100 questions to EWG**
- **EWG consolidated related questions**
- **25 Q&As were finally included in this *Step 2* document**

Table of Contents

- **Q&A document is structured according to the original guideline**
  - Section 1 Introduction 4 Q&As
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Q&As section 1

- **Clarification of meaning of mutagenic and genotoxic potential**
- **Recommendations for evaluation of impurities present at or below 1 mg**
- **Recommendations for evaluation of impurities present above 1 mg**

Q&As sections 2 & 3

- **Are semi-synthetic drugs in scope?**
  - Yes, for certain cases, e.g. introducing mutagenic impurities with specific manufacturing steps.
- **Should non-mutagenic carcinogens and mutagenic non-carcinogens be controlled by ICH M7?**
  - Non-mutagenic carcinogens are out of scope
  - Mutagenic impurities that are proven non-carcinogens are considered similar to class 5 impurities.

Q&As sections 4 & 5

- **What does "significant increase in clinical dose of marketed products" mean?**
  - Any increase in dose that would increase any mutagenic impurity above acceptable limits

Q&As sections 6

- **Recommendations for validation and documentation to provide for in-house or not commonly used (Q)SAR models**
- **Expectations for qualification of an (Q)SAR "out of domain" or "non-coverage" result to assign an impurity to Class 5**
- **AMES negative impurities with positive clastogenicity study results:**
  - Irrelevance of clastogenicity test for classification
- **Rationale for follow up assays in *Note 3***

Q&A section 7

- **Ames positive impurities**
  - Further qualification using *in vivo* mutation assays can be performed to demonstrate lack of *in vivo* relevance
  - *In vivo* mutation assays not considered sufficiently validated to derive compound specific limits
- **LTL approach not considered acceptable for PDEs**
- **HIV disease has been moved from "treatment duration <10 years" to "lifetime" treatment**
  - Explanations and Implications
- **Limits for individual impurities apply when three or more class 2 and class 3 impurities are present**

Q&As section 8

- **Option 4 control strategy**
  - When is it appropriate?
  - Elements recommended when using predictive purge calculations to claim no analytical testing as per option 4
- **Considerations for control of impurities introduced or formed in the last synthetic step**
- **When is periodic verification testing allowed?**

Q&As section 8 cont.

- **Does level of impurities consistently found <30% TTC in multiple batches justify no testing?**
- **Batch scales recommended to provide experimental data to support control options 3 and 4**

Q&As section 9

- **Are (Q)SAR predictions made earlier in development still valid for market authorization?**
- **Recommendations for clarity of ICH M7 risk assessment and control strategy**
  - Location in CTD
  - Details to be provided in modules 2, 3 and 4

Conclusions

- **Q&As are provided to minimise different interpretation of specific aspects of**
  - Risk assessment of mutagenic impurities
  - Control strategy of mutagenic impurities
- **Q&As aim to further harmonize and facilitate the implementation of ICH M7 recommendations**

Contact

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

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