

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

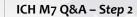
International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use



ICH M7 Q & A - Step 2

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#### **Outline**

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

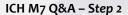
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### **Background**

- 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 19<sup>th</sup> 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

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#### **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
  - Section 2 Scope 1 Q&A
  - Section 3 General Principles 2 Q&As
  - Section 4 Marketed products 1 Q&A
  - Section 6 Hazard Assessment 4 Q&As
  - Section 7 Risk Assessment 5 Q&As
  - Section 8 Control 6 Q&As
  - Section 9 Documentation 2 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.

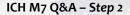
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# Q&As sections 4 & 5

- 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:
  - o Irrelevance of clastogenicity test for classification
- Rationale for follow up assays in Note 3

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#### **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</li>
  - 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?

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### **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

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### **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

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# **Contact**

For any questions please contact the ICH Secretariat:

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