TESTING FOR CARCINOGENICITY OF PHARMACEUTICALS S1B(R1)

Step 2

Step 2 document – to be released for comments

Date 10 May 2021

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

Legal Notice

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Background

- **This document has been signed off as a *Step 2* document (10 May 2021) to be issued by the ICH Regulatory Members for public consultation**
- **This document was developed based on a Concept Paper (14 Nov 2012) and a Business Plan (14 Nov 2012)**
- **This document is supported by scientific advances since S1B was adopted, several retrospective analyses of pharmaceutical datasets, and an independent international prospective study conducted by the ICH S1 EWG confirming that an integrated WoE approach could be applied to adequately assess the human carcinogenic risk for certain pharmaceuticals in lieu of conducting a 2-year rat study without compromise to patient safety.**
- **Anticipating finalization as a *Step 4* document to be implemented in the local regional regulatory system: May / 2022**

Key Principles

- **These changes to S1 introduce a more comprehensive and integrated approach to addressing the risk of human carcinogenicity of small molecule pharmaceuticals.**
- **Under this revised approach the need for 2-year rat studies are not always warranted. The need for a study can be evaluated on a case-by-case basis to determine whether a carcinogenicity assessment can be accepted in lieu of conducting a 2 year study.**
- **Clarification is provided on the criteria for deciding whether the conduct of a 2-year rat carcinogenicity study of a given pharmaceutical would add value to this risk assessment.**

Guideline Scope and Objectives

- **Scope: all small molecule pharmaceuticals where carcinogenicity evaluations are recommended as described in ICH S1A.**
- **Objectives:**
  - **Expand the testing scheme for assessing human carcinogenic risk by introducing an integrative approach that provides specific weight of evidence [WoE] criteria that inform whether a 2-year rat study would add value in completing a human carcinogenicity risk assessment.**
  - **Add a plasma exposure ratio-based approach for setting the high dose in the rasH2-Tg alternative mouse model.**

Implications and Benefits

- **Encourages a more scientifically based approach to carcinogenicity risk assessment of small molecules starting earlier in development.**
- **Reduces the number of 2-year rat carcinogenicity studies with associated savings in animal use, costs and timelines.**

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Cross-references to other Relevant Guidelines

- **This Addendum is to be used in close conjunction with ICH *S1A Guideline on the Need for Carcinogenicity Studies for Pharmaceuticals, S1B Testing for Carcinogenicity of Pharmaceuticals, and S1C(R2) Dose Selection for Carcinogenicity Studies*.**
- **The Addendum references ICH *S2(R1) Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use*, and ICH *S8 Immunotoxicity Studies for Human Pharmaceuticals* when conducting the WoE assessment.**
- **The Addendum extends to small molecule pharmaceuticals the principles modelled for carcinogenicity assessment of biotechnology-derived pharmaceuticals by ICH *S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals.***

Summary of Guideline Content

An integrative WoE assessment approach as described in sections 2.1 and 2.2 may support a conclusion that the test compound is either:

- **likely to be carcinogenic in humans such that the product would be labeled accordingly and any 2-year rat carcinogenicity studies would not add value; or**
- **likely not to be carcinogenic in humans such that a 2-year rat study would not add value (may also not be carcinogenic in rats, or may likely be carcinogenic in rats but through well recognized mechanisms known to be human irrelevant); or**
- **uncertain with respect to the carcinogenic potential for humans, and a 2-year rat carcinogenicity study is likely to add value to human risk assessment.**

Summary of Guideline Content (continued)

Section 2.1: The WoE approach is based on a comprehensive assessment of the totality of data relevant to carcinogenic potential available from public sources and from conventional drug development studies, including:

1) **data that inform carcinogenic potential based on drug target biology and the primary pharmacologic mechanism of the compound including carcinogenicity information available on the drug class,**
2) **results from secondary pharmacology screens, especially those that inform carcinogenic risk,**
3) **histopathology data from repeated-dose toxicity studies completed with the test agent, with particular emphasis on the long term rat study including exposure margin assessments,**
4) **evidence for hormonal perturbation,**
5) **genetic toxicology study data using criteria from ICH S2(R1),**
6) **evidence of immune modulation in accordance with ICH S8.**

Summary of Guideline Content (continued)

Where one or more WoE factors may be inconclusive or indicate a concern, the Sponsor can conduct additional investigations that inform human relevance, such as:

1) **special studies, or analyses of specimens collected from prior studies, and**
2) **clinical data generated specifically to inform human mechanistic relevance at therapeutic exposures.**

Summary of Guideline Content (continued)

Section 2.2: While all factors contribute to the integrated analysis, the relative importance of each factor will vary depending on the specific molecule being considered.

- **An established profile of other compound(s) in a drug class contributes substantially to assessing human carcinogenic risk associated with the drug target.**
- **While compounds with novel drug targets (i.e., first-in-class) are considered eligible for an integrative WoE-based approach, a higher evidentiary standard is expected to establish no cause-for-concern.**
- **Case Study examples are provided in Appendix 1 demonstrating how the WoE factors can be integrated in determining the need for a 2-year rat study.**

Summary of Guideline Content (continued)

Section 3: A plasma exposure (AUC) ratio for high dose selection in the rasH2-Tg model has not been globally accepted as an endpoint since the model was introduced under S1B.

- **A comprehensive analysis of experience in the rasH2-Tg mouse model was completed and indicates that there is no value in exceeding a 50-fold plasma AUC exposure ratio (rodent:human) to support carcinogenicity assessment.**
- **All criteria for selection of the high dose for carcinogenicity studies as specified in S1C(R2) for 2-year rodent studies are applicable to rasH2-Tg, including an AUC plasma exposure ratio, except that the exposure ratio will be 50-fold in rasH2-Tg rather than 25-fold as for 2-year studies conducted in wild type rodents.**

Considerations

- **When the Sponsor's WoE assessment concludes that conduct of a 2-year rat study is not warranted, the Sponsor should seek alignment with the Drug Regulatory Agency [DRA] of each region where marketing approval is sought.**
- **When a Sponsor decides alternatively to conduct a 2-year rat study in accordance with ICH S1B, there is no obligation to seek concurrence nor to document their rationale with each DRA.**
- **A carcinogenicity study in mice, either 2-year or a short-term transgenic model as specified in ICH S1B, remains a recommended component of a carcinogenicity assessment except in unusual circumstances (e.g., only subtherapeutic pharmacologically inactive test exposures are achievable).**

Conclusions

- **S1B(R1) introduces a more scientifically based and integrated approach to assess the human carcinogenic risk for small molecule pharmaceuticals, using WoE criteria evaluated on a case-by-case basis in lieu of always conducting a 2-year rat study.**
- **A plasma exposure AUC ratio of 50-fold is an acceptable criteria for high dose selection for carcinogenicity studies in rasH2-Tg mice.**

Contact

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