TESTING FOR CARCINOGENICITY OF PHARMACEUTICALS S1B(R1)

Step 4

Step 4 document – to be implemented

9 August 2022

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

Legal Notice

Background

- **This document has been signed off as *Step 4* document (4 August 2022) to be implemented by the ICH Regulatory Members.**
- **This document was developed based on a Concept Paper (14 Nov 2012) and a Business Plan (14 Nov 2012).**
- **The Addendum to ICH S1B 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 integrative Weight of Evidence (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.**

Key Principles

- **This Addendum to ICH S1B introduces a more comprehensive and integrative approach to assessing human carcinogenic risk of pharmaceuticals.**
- **This integrative approach describes specific WoE criteria that in some cases may provide an adequate assessment of human carcinogenicity risk without data from a 2-year rat carcinogenicity study.**
- **The Addendum encourages a more mechanism-based human carcinogenicity risk assessment and may reduce the use of animals in accordance with 3R (reduce/refine/replace) principles while continuing safe and ethical development of new pharmaceuticals.**

Guideline Objectives 1/2

- **Scope: all 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 WoE criteria that inform whether a 2-year rat study is likely to add value to a human carcinogenicity risk assessment.**
  - **Encourage a more mechanism-based approach to human carcinogenicity risk assessment of pharmaceuticals starting earlier in drug development.**

Guideline Objectives 2/2

- **Objectives (continued):**
  - **Reduce the use of animals in accordance with the 3R principles and shift resources to focus on generating more mechanism-based carcinogenicity assessments, while continuing to promote safe and ethical development of new pharmaceuticals.**
  - **Add a plasma exposure ratio-based approach for setting the high dose in the rasH2-Tg alternative mouse model.**

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Summary of Guideline Content 1/7

- **This Addendum is to be used in close conjunction with ICH *S1A Guideline on the Need for Carcinogenicity Studies of Pharmaceuticals, S1B Testing for Carcinogenicity of Pharmaceuticals, and S1C(R2) Dose Selection for Carcinogenicity Studies of Pharmaceuticals*.**
- **The document references ICH *S2(R1) Guidance on 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 all pharmaceuticals needing carcinogenicity testing as described in ICH S1A Guideline 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 2/7

An integrative WoE assessment approach as described in Sections 2.1 and 2.2 may support a conclusion that the carcinogenic potential of a pharmaceutical in humans is either:

- **likely, such that a 2-year rat carcinogenicity study would not add value; or**
- **unlikely, such that a 2-year rat study would not add value; or**
- **uncertain, such that a 2-year rat carcinogenicity study would add value to human risk assessment.**

Summary of Guideline Content 3/7

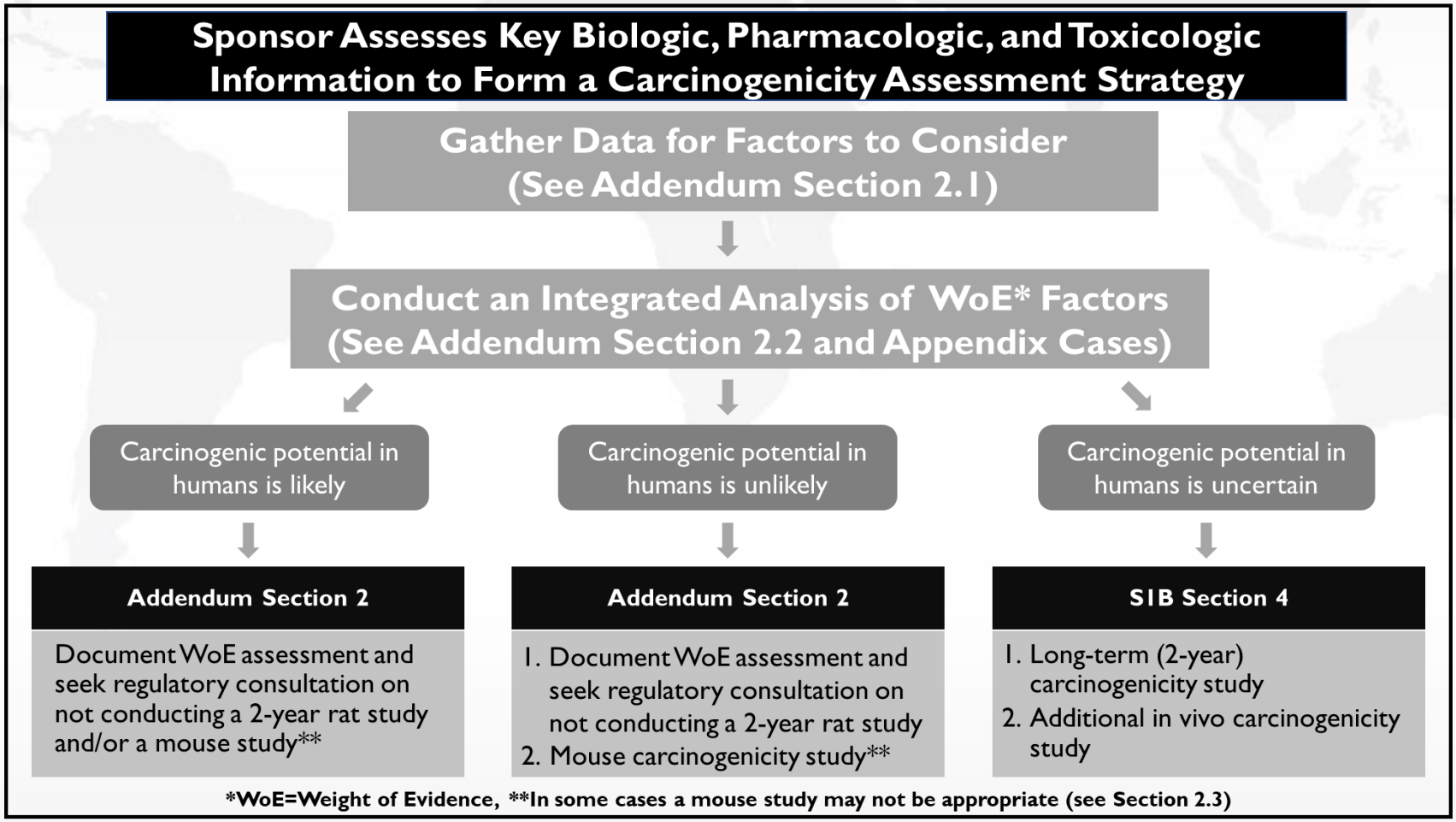

Figure 1: Flow scheme outlining key steps and options in developing a carcinogenicity assessment strategy and determining the added value of a 2-year rat study.

Summary of Guideline Content 4/7

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 relevant drug development studies, including:

1) **data that inform carcinogenic potential based on drug target biology and the primary pharmacologic mechanism of the parent compound and major human metabolites including carcinogenicity information on class effects,**
2) **results from secondary pharmacology screens, especially those that inform carcinogenic risk,**
3) **histopathology data from repeated-dose toxicity studies completed with the compound, with particular emphasis on the 6-month rat study including plasma 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 5/7

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

- **An established profile of other compound(s) in a drug class contributes substantially to assessing human carcinogenic risk associated with modulation of the pharmacologic target.**
- **While compounds with novel drug targets (i.e., first-in-class) are considered eligible for an integrative WoE assessment, further evidence that there is no cause-for-concern in regard to target biology is needed to compensate for the lack of precedent.**
- **Case Study examples are provided in the Appendix demonstrating how the WoE factors can be integrated to determine the value of conducting a 2-year rat study for assessment of human carcinogenic risk.**

Summary of Guideline Content 6/7

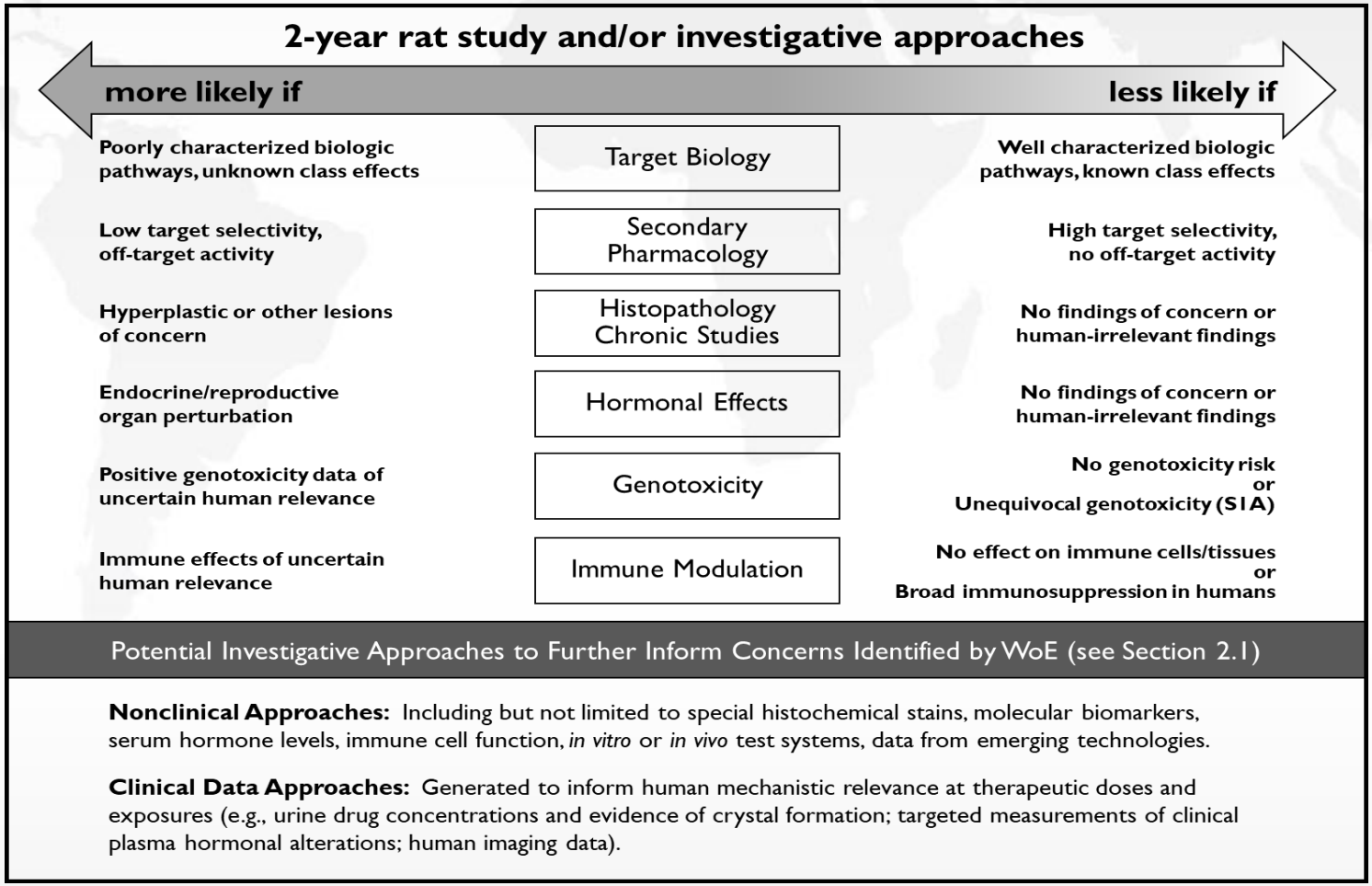

Figure 2: Integration of key WoE factors and potential investigative approaches to further inform on the value of conducting a 2-year rat study for assessment of human carcinogenic risk.

Summary of Guideline Content 7/7

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

- **A retrospective evaluation of available data derived from the rasH2-Tg mouse model was completed and indicates that a 50-fold plasma exposure (AUC) ratio (rodent:human) is an adequate criterion for high dose selection.**
- **All criteria for selection of the high dose for carcinogenicity studies as specified in ICH S1C(R2) for 2-year rodent studies are applicable to rasH2-Tg mice, including a plasma exposure (AUC) ratio, except that the plasma exposure ratio will be 50-fold in rasH2-Tg mice rather than 25-fold as for 2-year studies conducted in standard strains of rodents.**

Considerations 1/2

- **When the WoE assessment supports a conclusion that conduct of a 2-year rat study does not add value to the assessment of human carcinogenic risk, the sponsor should seek consultation with the applicable Drug Regulatory Agency (DRA) in accordance with the established regulatory procedure for that region.**
- **When a sponsor decides to conduct a 2-year rat study in accordance with ICH S1B, there is no obligation to seek consultation with the DRA.**

Considerations 2/2

- **A carcinogenicity study in mice, either a 2-year study in a standard strain or a short-term study in a transgenic model as in ICH S1B, remains a recommended component of a carcinogenicity assessment plan.**
- **There are cases where it may not be appropriate to conduct a mouse carcinogenicity study such as when:**
  - **the WoE assessment strongly indicates no carcinogenic risk to humans and the data indicate that only subtherapeutic and pharmacologically inactive drug levels relative to human exposure can be achieved in the mouse, or**
  - **the WoE assessment indicates that a compound is likely to be carcinogenic in humans.**

Guidelines for Implementation

- **With the implementation of the S1B(R1) Addendum, it is anticipated that industry will generate and submit a WoE-based carcinogenicity assessment for DRA consideration when a sponsor concludes that a 2-year rat study does not add value to human carcinogenicity risk assessment.**
- **A 50-fold plasma exposure (AUC) ratio will be considered as an adequate criterion for high dose selection in the rasH2-Tg mouse model along with other criteria specified in ICH S1C(R2).**

Conclusions

- **ICH S1B(R1) introduces a more integrated approach to assess the human carcinogenic risk of 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 adequate criterion for high dose selection for carcinogenicity studies in the rasH2-Tg mouse model.**

Contact

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