

Final Concept Paper S1B(R1) Testing for Carcinogenicity of Pharmaceuticals

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Endorsed by the Management Committee on 26 March 2024

1. Type of Harmonisation Action Proposed:

The S1B(R1) EWG recommends its transition to an Implementation Working Group (IWG) to share experiences regarding ongoing implementation efforts for the new S1B(R1) weight of evidence (WoE) approach for carcinogenicity assessments, to develop potential best practices, and to provide counsel to parties regarding implementation issues. The IWG would hold regular but infrequent meetings, as outlined below, for a period of three years.

An IWG is necessary to promote the goal of harmonization and bolster the success of ICH's investment in the WoE approach developed by scientific experts from regulatory authorities and industry collaborating for more than a decade. Given the significant resources invested to date and the potential for inconsistent conclusions identified during the prospective study and following finalisation of the S1B(R1) Guideline, explicit monitoring of implementation of the WoE approach is recommended to identify any areas of inconsistency and discuss how they can be addressed. It should be noted that if even one region requires animal studies that the other regions are aligned accepting a WoE assessment, this will still generate additional studies, diminishing the goal of minimizing such animal studies and reducing regulatory burden.

All parties currently participating in the S1B(R1) EWG will be invited to participate on the IWG. Participation will be voluntary.

The full IWG would be convened by teleconference by the S1B(R1) Rapporteur party on a regular, but infrequent basis, approximately once per year. Additional meetings by teleconference including only S1B(R1) Drug Regulatory Authorities (DRAs) who have mutual confidentiality agreements in place would be held approximately twice per year to share confidential information to discuss the WoE submissions received in each region, corresponding decisions to accept or reject WoE assessments *in lieu* of a 2-year rat study and supporting rationales.

The IWG would be established in January 2024. Periodic teleconferences will be held to:

- Exchange information among DRAs with confidentiality agreements in place to establish the extent of regulatory alignment and share experiences in evaluating WoE submissions.
- Exchange anonymized information across the full IWG membership while maintaining confidentiality to discuss the extent of alignment in the review of WoE submissions based on DRA and industry perspectives.

- Identify areas of inconsistency in evaluating WoE submissions and discuss ways to increase consistency, if warranted.
- Identify issues to be addressed in a potential, future Q&A document.

2. Background to the Proposal:

The ICH S1B(R1) addendum expands the evaluation process for assessing human carcinogenic risk of pharmaceuticals by introducing an additional approach that is not described in the original ICH S1B. This is 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. This integrative approach reduces the use of animals in accordance with the 3R (reduce/refine/replace) principles and shifts resources to focus on generating more scientific mechanism-based carcinogenicity assessments.

3. Background to the Proposal and Expected Deliverable(s):

Consistent and effective implementation of the S1B(R1) addendum by multiple DRAs is essential to realize the addendum's benefits. Preliminary information shared between industry and DRAs has identified cases of different decisions by DRAs from evaluation of WoE submissions. While complete regulatory alignment is not an expectation, this observation highlights the importance of continued exchange of information among members to ensure that a reasonable degree of alignment is achieved during this early period of implementation. The role of the IWG will be to advance implementation by providing expert resources, insight, and guidance to promote harmonization. As part of these efforts, the IWG may identify or support regional implementation efforts (e.g., training, conferences, publications).

4. Planning:

After establishment and commencing work the IWG will conclude operations after a three-year period. The IWG's continued operation will be evaluated on an annual basis, during the three-year period by the ICH Management Committee.

Impact of the Project:

S1B(R1) implementation is expected to take several more years as regional and regulatory changes are adopted. During this time, the IWG will discuss how to overcome common implementation challenges and promote consistency in the evaluation of WoE submissions. Similarly, the IWG will serve as an effective platform to monitor implementation by industry and to disseminate feedback on proper application of the concepts described in the S1B(R1) addendum.