Provisional Translation (as of March 2025)*

Points to consider for the discussion with PMDA using the ICH S1B (R1) guideline and in the approval application
(Early Consideration)

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1. Introduction

Considering the ICH S1B (R1) guideline[1)] which was issued based on the agreement reached at ICH, it is possible to conclude whether a 2-year rat carcinogenicity study adds value to the assessment of human carcinogenicity risk by comprehensively evaluating the weight of evidence (WoE evaluation) for various factors related to carcinogenicity, such as the biological properties of the drug target/primary pharmacological effects of the parent compound and its major human metabolites, secondary pharmacological effects of the parent compound and its major human metabolites, and histopathological data from a 26-week repeated-dose toxicity study in rats, including exposure margins of the parent compound and its major human metabolites[2)], hormonal fluctuations, genotoxicity, and immune regulation, which are obtained from nonclinical studies of drugs under development and publicly available information. When evaluating the carcinogenicity of drugs, carcinogenicity studies have usually been conducted in two species (rat and mouse). However, the ICH S1B(R1) guideline presents a new concept of carcinogenicity evaluation based on WoE evaluation, which is expected to contribute to the promotion of safe and ethical drug development while avoiding low value-added studies on human safety from the perspective of 3Rs (replacement, reduction and refinement. Intended to use alternative methods, reduce the number of animals used, and reduce animal pain).

A domestic notification regarding the ICH S1B(R1) guideline[3)] was issued in Japan in March 2023. At the same time, a safety consultation related to the S1B (R1) guideline for drugs (S1B (R1)

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* This English version of the Japanese Early consideration is provided for reference purposes only. In the event of any inconsistency between the Japanese original and the English translation, the former shall prevail.

1) ICH Harmonised Guideline. S1B (R1): Testing for Carcinogenicity of Pharmaceuticals (4 August 2022)

2) Generally, the margin of exposure is calculated using the group mean of the area under the concentration-time curve (AUC) in animals and the group mean of the AUC at the maximum recommended human dose (MRHD). In some cases, however, calculation based on the group mean of the maximum plasma concentration (Cmax) may be more appropriate than AUC.

3) Notification: PSEHB/PED No. 0310/1: Revision of the Guidelines for Carcinogenicity Testing of Pharmaceuticals, 10- Mar-2023 (in Japanese)

consultation)[4] was newly established at the Pharmaceuticals and Medical Devices Agency (PMDA), which made it possible to discuss with the PMDA on the appropriateness of exemptions from the rat carcinogenicity study based on the ICH S1B (R1) guideline. Based on the ICH S1B (R1) guideline, drug developers should thoroughly review the results and published information on the WoE elements of the drug under development and select a development strategy, either waiving a rat carcinogenicity study based on the WoE evaluation or performing two conventional carcinogenicity studies (rat and mouse) based on the timing of the approval application. If the former is selected, the appropriateness of the WoE evaluation should be discussed with PMDA.

Based on the above points, this document provides the considerations for discussion with PMDA utilizing the S1B (R1) consultation and at the time of approval applications.

2. Points to consider for the discussion with PMDA using the ICH S1B (R1) guideline and in the approval application

When conducting S1B(R1) consultations, the following points should be noted:

1) A pre-consultation meeting is required, and an application for an S1B (R1) consultation can only be made if it is determined that an S1B (R1) consultation is possible based on the materials submitted at the pre-consultation meeting and the issues outlined at the pre-consultation meeting.
2) Consultation materials for an S1B (R1) consultation must be submitted approximately 13 weeks before the S1B (R1) consultation.
3) Consultation materials for an S1B (R1) consultation must be submitted approximately 13 weeks prior to the consultation date for S1B (R1) consultations.

For detailed procedures for S1B(R1) consultations, please refer to Attachment 1-2 of the latest PMDA implementation guidelines[5] and website[4].

In addition, this document provides a Q&A format for points of consideration when conducting S1B (R1) consultations and submitting approval applications. However, please note that the points listed in this document are subject to review from time to time.

Q1. What kind of materials should be submitted for the pre-consultation meeting (required)?

In the pre-consultation meeting (required), as part of the arrangement of the points before the S1B (R1) consultation, PMDA will provide comments focusing on items that are insufficiently explained in the consultation material (draft), and therefore, the PMDA recommends submitting the consultation

[4] Pharmaceuticals and Medical Devices Agency. "Drug Safety Consultation (Consultation on ICH S1B (R1) Guideline)", (in Japanese) https://www.pmda.go.jp/review-services/f2f-pre/consultations/0117.html.
[5] PMDA Notification No. 0302070 of the Chief Executive, dated March 2, 2012. (in Japanese) https://www.pmda.go.jp/files/000219237.pdf. Attachment 1-2 of the Notification of Implementation Guidelines. (in Japanese) https://www.pmda.go.jp/files/000251251.pdf.

material (draft) whenever possible. If it is difficult to submit the consultation materials (draft), it is possible to submit an outline of the consultation materials (including supplementary explanations of outline). However, it should be noted that if there are many issues in arranging the issues at the pre-consultation meeting, PMDA may ask drug developers to prepare the materials to resolve the issues and request to hold the pre-consultation meeting again.

In addition to the following matters in Attachment 1-2 of the latest PMDA implementation guidelines[5], please describe the explanation of whether the drug target is novel, the reason for setting the highest dose based on "Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals, ICH M3 (R2)" (February 19, 2010, PFSB/ELD Notification No.0219-4) for the 26-week repeated dose toxicity study in rats, histopathological findings including changes that were judged to be of no toxicological significance and the discussion by drug developers regarding each WoE evaluation in the consultation material. In addition, when using literature to discuss various elements related to WoE, it is necessary to provide an outline of the literature and to be clear about the considerations. With regard to literature on the carcinogenic modification related to the biological properties and primary pharmacological action of the drug target, please research literature related to the promotion and inhibition of carcinogenic potential and include the contents of those in the consultation materials. Please note if drug developers wish to deny findings of concern, they are required to provide detailed explanations.

Implementation guideline for S1B (R1) consultation (excerpt)

9. Contents to be included in consultation materials

- Material outlining the history that led to implementation of the S1B (R1) consultation, background of drugs, the results of each element related to the WoE approach and its interpretation (Japanese material; in addition to Japanese material, English material should also be submitted if possible).
- List compared between systemic exposure (Cmax, AUC, etc.) of the active ingredient in the proposed approved dosage and administration and systemic exposure (Cmax, AUC, etc.) at each dose level (including the NOAEL and maximum dose) in the pivotal toxicity studies. List comparing systemic exposure of metabolites, if there is concern for metabolites (if corresponding lists are included in the Investigator's Brochure, etc., it can be replaced with those lists).
- Materials that support the consultation materials (final reports, literature and information, knowledge of the results of carcinogenicity studies of drugs with similar mechanisms of action, and other materials that contribute to explanations)
- Latest investigator's brochure
- Results of decisions made by foreign regulatory authorities regarding exemptions from the rat carcinogenicity study based on ICH S1B (R1) and the data submitted on which the decision was based (if applicable)

Q2. When applying for an S1B (R1) consultation, is it possible to discuss the need for a 2-year rat carcinogenicity study based on the results of rat available at that time early in development when the results of a 26-week repeated dose rat toxicity study have not yet been obtained? For example, if a 13-week rat repeated dose toxicity study has been completed, but a 26-week rat repeated dose toxicity study has not been conducted or is currently being conducted, is it possible to apply an S1B (R1)

consultation on the assumption that no concerns were raised in the 26-week rat repeated dose toxicity study?

It is difficult to apply for an S1B(R1) consultation when the final report of the 26-week repeated dose toxicity study in rats has not yet been obtained. The ICH S1B (R1) guideline places special emphasis on the results and consideration based on histopathological examinations from 26-week repeated-dose toxicity studies in rats to predict the carcinogenicity of a 2-year rat carcinogenicity study. Therefore, when applying for an exemption from a 2-year rat carcinogenicity study based on the WoE evaluation of the ICH S1B (R1) guideline, please request the pre-consultation meeting (required) after obtaining the final report of the 26-week rat repeated-dose toxicity study.

Q3. If it has been decided from the very start of the drug development that a 2-year rat carcinogenicity study will be conducted, is it still necessary to discuss a WoE evaluation?

The ICH S1B (R1) guideline recommends that all developed products requiring carcinogenicity studies under the ICH S1A guideline should be evaluated in a WoE evaluation to determine whether a rat carcinogenicity study should be conducted for 2 years. Therefore, conducting a 2-year rat carcinogenicity study without adequate WoE assessment is not recommended from the perspective of the 3Rs. If it is determined for drug developers to conduct a 2-year rat carcinogenicity study based on the WoE evaluation, the rationale for the study should be retained, and the background conducting of a 2-year rat carcinogenicity study should be described in the CTD section 2.6.6 and/or the report of a 2-year rat carcinogenicity study. It is not necessary to obtain the PMDA's agreement on the appropriateness of the policy to conduct a 2-year rat carcinogenicity study prior to the study.

Q4. Regarding the consultation of the omission of the 2-year rat carcinogenicity study based on the WoE evaluation of ICH S1B (R1) guideline, is it acceptable to consult with only one authority even in the case of global development?

The consultation of exemption from a 2-year rat carcinogenicity study based on a WoE assessment of ICH S1B (R1) guidelines need to be discussed for each regulatory authority submitting a marketing application. Therefore, it should be noted that there may be discrepancies between the regulatory authorities.

Q5. When repeated dose toxicity studies are conducted in mice, the longest repeated dose toxicity study in rats has traditionally been a 13-week study as a dose finding study for rat carcinogenicity study, but in the future, a 26-week test may be an option in anticipation of the omission of the 2-year rat carcinogenicity study. Is it acceptable to conduct a 26-week study in rats instead of a 13-week study as a dose finding study for carcinogenicity testing?

If the results obtained are sufficient to aid in dose finding for a 2-year rat carcinogenicity study, the

26-week rat study can be used as a dose finding study for the 2-year rat carcinogenicity study.

Q6. What should be done if new results or information are obtained after the S1B(R1) consultation has determined that a 2-year rat carcinogenicity study is unnecessary?

After the S1B (R1) consultation has been determined not to require a 2-year rat carcinogenicity study, if new results or information that may be relevant to the concern for carcinogenicity is obtained, it is necessary to evaluate the effect of the new results or information on the performed WoE assessment and to review the need for a 2-year rat carcinogenicity study. Examples of information that may be relevant to carcinogenic concerns include, but are not limited to, the following:

<example>

- Positive results of the mouse carcinogenicity study of the developed drug
- New information on the biological properties/pharmacological mechanism of the drug target of the developed drug (including information on carcinogenicity of other drugs with the same pharmacological mechanism of action)
- Information on tumorigenesis in clinical studies of developed drug

It is also recommended that the results of the WoE reevaluation be discussed with the PMDA, as appropriate, so that differences between drug developers and the PMDA do not affect the development schedule or the approval application for the drug.

Q7. If the 2-year rat carcinogenicity study is deemed insignificant according to the ICH S1B(R1) guideline, in which module should the carcinogenicity assessment report based on the WoE evaluation be stored when applying for the approval application?

If a 2-year rat carcinogenicity study is exempted in accordance with the ICH S1B(R1) guideline, a carcinogenicity assessment report based on the WoE evaluation should be stored in "Module 4.2.3.4, Rodent Carcinogenicity" after preparing a carcinogenicity assessment report describing the background and reasons for the decision to exempt the rat carcinogenicity study based on the WoE evaluation. In addition, results of WoE assessment should be provided in CTD section 2.6.6. Related to Q6, if new results or information is obtained after a 2-year rat carcinogenicity study is deemed unnecessary in the S1B (R1) consultation, an updated new carcinogenicity assessment report based on the WoE evaluation should be stored in "Module 4.2.3.4, Rodent Carcinogenicity."