The ICH S1 Regulatory Testing Paradigm of Carcinogenicity in rats.

4th Status Report - August 2021

Jan Willem van der Laan (EC, Europe, Regulatory Chair), Todd Bourcier (FDA, United States), Tania Cavaliero (Swissmedic, Switzerland), Tim McGovern (FDA, United States), Akiyoshi Nishikawa (MHLW/PMDA, Japan), Jihei Nishimura (MHLW/PMDA, Japan), Kumiko Ogawa (MHLW/PMDA, Japan), Markku Pasanen (EC, Europe), Geoffrey Ebere (Health Canada, Canada), Alisa Vespa (Health Canada, Canada)

Introduction & Background

The ICH S1 Expert Working Group (EWG) has convened regularly to discuss the status of the prospective evaluation study which started in August of 2013 with the publication of the Regulatory Notice Document (RND). As of June 2021, Drug Regulatory Authorities (DRAs) received and reviewed all anticipated 45 Final Study Reports (FSRs) from completed 2-year rat studies. The S1 EWG has jointly discussed these cases in Montreal (2017), Charlotte (2018) and by virtual meetings thereafter.

In March 2020, the 5 DRAs assessed 42 Carcinogenicity Assessment Document (CAD)-FSR datasets available at that time to preliminarily evaluate the relative contribution of each Weight-of Evidence (WoE) attribute that most appropriately identified scenarios where a WoE approach in a CAD would provide a feasible alternative to a 2-year rat bioassay. A publication is planned which will include an assessment of all 45 CAD-FSR datasets. This assessment supported the WoE approach included in the Step 1 draft Addendum to S1B(R1).

A CAD addresses the carcinogenic potential of an investigational pharmaceutical using a WoE approach that addresses specific criteria and, based on the level of certainty of carcinogenic risk and its potential human relevance, a sponsor indicates the need for and additional value of conducting a 2-year rat study. Each participating DRA independently reviewed the submitted CADs and the rationale for concurrence or non-concurrence with the sponsor's assessment was documented. As the 2-year rat studies were completed and results submitted to the DRAs as FSRs, the study outcome was then checked against the WoE assessment in the respective CAD. Results on the accuracy of prospective assessments, the relative value of the WOE attributes, and the degree of concordance among all parties are anticipated to help define the conditions under

which a WoE evaluation sufficiently characterizes the risk of human carcinogenicity without conducting a 2-year rat carcinogenicity study.

State of the Prospective Evaluation Study

Part 1: Update on CAD and Final Study Report Submissions

The acceptance period for CAD submissions closed on 31 December 2017. A total of 48 CADs submitted by 22 sponsors have been reviewed and categorized by DRAs. Participating sponsors were subsequently informed that the acceptance period for submission of the corresponding FSR would close on 31 December 2020. As of that date, the DRAs received 45 FSR submissions of which all have been evaluated by the S1 Expert Working Group as of June 2021. The participating sponsors indicated that the FSR for 3 CADs would not be submitted.

In the 2016 RND revision, a threshold of 20 complete Category 3 cases (i.e., CAD + FSR) was considered necessary to allow a decisional analysis by the EWG. This threshold was surpassed with completion of 24 Category 3 cases as of the 31 December 2020 closing date.

CAD Categories and Concordance

The RND directed sponsors to classify their investigational compound into one of the following categories in the CAD:

- *Category 1: Highly likely to be carcinogenic in humans, such that rodent carcinogenicity studies would not add value.*
- *Category 2: Uncertain carcinogenic potential, such that rodent carcinogenicity studies are likely to add value.*
- *Category 3a: Highly likely to be carcinogenic in rats through prior established and well-recognized mechanisms known to be human irrelevant, such that a rat carcinogenicity study would not add value.*
- *Category 3b: Highly unlikely to be carcinogenic in both rats and humans, such that a rat carcinogenicity study would not add value.*

Table 1 summarizes the categories designated by the sponsors and the corresponding category designation by the DRAs of the 45 completed CAD/FSR cases. Sponsors designated Category 3a or 3b for 31 cases. At least one DRA concurred with the sponsor's designation of Category 3a/b in 24 of these cases (77%). As not all Category 3a/b designations by DRAs were unanimous, Table 2 summarizes the extent of concordance among the participating DRAs in agreeing with the sponsor's designation of Category 3a/b. The DRAs were unanimous in concurring with a Category 3a/b designation in 12 cases and remained split, typically between Categories 2 & 3, in 12 cases.

Table 1: Category designation by Sponsors and DRAs for completed CAD-FSR Cases

Category	Number of CADs	
	Sponsor	DRAs
1	3	3
2	11	18
3a/b	31	24
Total:	**45**	**45**

Table 2: Concordance among DRAs on Sponsor-proposed Category 3a/b designations for completed CAD/FSR cases

Category	Number of CADs			
	Sponsor	DRA		
		Unanimous	Split	DRA Total*
3a	14	7	5	12
3b	17	5	7	12
Total:	***31***	***12***	***12***	***24***

**DRA Total is lower than total sponsor's Category 3a/3b designations, as 7 were concluded by DRAs as Category 2.*

Part 2: Analysis of CADs in relation to Rat Carcinogenicity Study Outcome:

Note: A complete tabulation and discussion of data from the prospective evaluation period will be presented in a separate publication in support of revisions to ICH S1B.

The receipt of 24 complete Category 3 cases enabled the EWG to conduct a decisional analysis regarding the feasibility of applying a WoE approach as an alternative to conducting 2-year rat bioassays. Central to this analysis was evaluating the extent of consistency between the tumor outcome of the 2-year rat studies and the WoE evaluation provided in the CADs, with a particular focus on those CADs designated Category 3 by the sponsors and the DRAs. Also key to the

decisional analysis was examining the concordance of decisions made between the DRAs and sponsors and among the DRAs themselves, as a potential measure of future regulatory harmonization should a WOE alternative be adopted.

Based on evaluation of all Category 3 cases, the EWG concluded that the outcome of most though not all 2-year rat studies were consistent with the WoE evaluation provided in the associated CADs. Complete consistency between CADs and study outcomes was not an expectation of this prospective evaluation. For each case, key WoE attributes that the EWG considered of highest relevance to both categorization of a CAD and to the rat study outcome were identified. For cases where inconsistenices with the rat study outcome were observed, the EWG conducted a retrospective analysis to identify information in the pharmacology or toxicology data to refine the WoE criteria that should be addressed in a CAD. Differences in data interpretation and weighting of WOE attributes were expected to result in differences in categorization of CADs which were indeed observed during the study (Table 2). The EWG recognized that focusing the analysis on cases where the sponsor and DRAs unanimously agreed that a WoE evaluation sufficiently characterized carcinogenic risk and was consistent with the 2-year rat study outcome would be most instructive in defining support for a WoE alternative with the greatest probability of regulatory concordance. From this analysis, the EWG identified the following WoE attributes which were more likely to support a conclusion that the results of a 2-year rat study would not add value to human carcinogenicity risk assessment.

- Target biology is well characterized and not associated with cellular pathways known to be involved with human cancer development. Often, the pharmaceutical target was non-mammalian and carcinogenicity data were available with the pharmacologic drug class.
- Results from chronic toxicity studies indicate no hyperplastic, hypertrophic, atypical cellular alterations, or degenerative/regenerative changes noted without adequate explanation of pathogenesis or human relevance, indicative of no on- or off-target potential of carcinogenic concern;
- No perturbation of endocrine and reproductive organs observed, or endocrine findings adequately explained with respect to potential human relevance;
- No identified concerns from secondary pharmacology screens intended to inform off-target potential for the pharmaceutical
- No evidence of immune modulation or immunotoxicity based on target biology and repeat dose toxicology studies
- The overall assessment of genotoxic potential is concluded to be negative based on criteria from ICH S2(R1) Guidance.

In the prospective evaluation study, 8 cases provided the data of a rasH2-Tg mouse study. Although rasH2-Tg mouse study results were recommended when available as a WoE element in the initial RND, the EWG's analysis of cases indicated that they did not significantly contribute to the prediction of the 2-year rat carcinogenicity study outcome. Therefore, results from a rasH2-

Tg mouse study are not considered a key WoE attribute in deciding the potential value of a 2-year rat study, and are not necessary to support a WoE assessment. However, if rasH2-Tg mouse study results are available, they should be discussed in the overall carcinogenicity assessment as supportive information.

Conclusion*: The DRAs/EWG concluded that results from the Prospective Evaluation Study can support pursuing an S1B addendum that describes a WoE-based assessment of carcinogenic risk for small molecule pharmaceuticals that have attributes similar to those observed in the unanimous Category 3 cases; however, for a significant number of programs, the 2-year rodent bioassay continued to provide value and remained the appropriate path.*