The ICHS1 Regulatory Testing Paradigm of Carcinogenicity in rats.

Status Report December 2017

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Introduction

The ICH-S1 Expert Working Group (EWG) convened in Montreal, Canada in May 2017 to discuss the status of the prospective evaluation study which started in August of 2013 with the publication of the Regulatory Notice Document (RND). This status report provides a brief overview of the study's progress and summary analysis of the first cohort of 2yr rat study outcomes in relation to their respective carcinogenicity assessment documents.

Background: The RND hypothesis and the Prospective Evaluation Study

The Regulatory Notice Document (RND) posted to the ICH website in August 2013 announced the start of a prospective evaluation study whereby sponsors voluntarily submit Carcinogenicity Assessment Documents (CADs). A CAD addresses the carcinogenic potential of an investigational pharmaceutical using a weight-of-evidence approach and, based on the level of certainty of carcinogenic risk and its potential human relevance, a company is expected to indicate the need for and additional value of conducting a 2yr rat study. Each participating Drug Regulatory Agency (DRA) independently reviews the submitted CADs and the rationale for concurrence or non-concurrence with the sponsor's assessment is documented. As the 2yr rat studies are completed and results submitted to the DRAs, the study's outcome is then checked against the weight-of-evidence assessment in the respective CAD. Results on the accuracy of prospective assessments and the degree of concordance among all parties are anticipated to help define the conditions under which a weight-of-evidence evaluation sufficiently characterizes the risk of human carcinogenicity without conducting a 2-yr rat carcinogenicity study.

In January 2016, a revised RND was posted to the ICH website to reflect recommendations made by the EWG following the December 2015 ICH convention in Jacksonville. The key revisions included the following:

- Extended by 2yrs the period for accepting CAD submissions, to the end of December 2017.

- Restricted acceptance of CADs to those written prior to month 14 of an ongoing 2yr rat study, effective June 2016.
- Allowed DRAs to request missing data considered pivotal to categorization of submitted CADs from participating sponsors.
- Planned a decisional analysis for S1 revision when the dataset includes 20 category 3 cases (i.e., CAD + study report). Category 3 cases were re-defined as those CADs where at least one DRA concurs with the sponsor that a WOE assessment sufficiently characterizes carcinogenic risk without conducting a 2yr rat study.
- Planned an interim analysis for futility when the dataset includes ≥6 category 3 cases and ≥10 category 2 cases.

State of the Prospective Evaluation Study (Dec 2017)

Part 1: Update on Submissions and closure of CAD submissions

As of December 31, 2017, a total of 46 CADs have been reviewed by the DRAs, of which 24 meet the definition of Category 3a or 3b. Two additional CADs, designated as Cat 3 by the Sponsor, have not yet been reviewed by the DRAs. This number of Category 3 CADs would allow for a decisional analysis by the EWG provided that at least 20 submit results of the rat carcinogenicity studies. To date, the DRAs have received and evaluated a total of 7 Category 3 cases where completed 2 year rat studies were available, among which 5 were discussed by the EWG in Montreal (Part 2).

Having met a reasonable number of CADs to feasibly achieve a decisional analysis, the EWG has closed the acceptance period for CAD submissions effective 31 Dec 2017. This Status Report, therefore, now explicitly confirms the expectation set in the January 2016 RND Revision that CAD submissions supporting the Prospective Evaluation Study are indeed terminated effective Dec 31, 2017.

CAD Categories and Concordance:

The RND directs Sponsors to classify their investigational compound into one of the following categories:

- *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 proposed by the Sponsors and the corresponding categories chosen by the DRAs after review and discussion of the 46 CADs submitted. Thirty-one CADs (67%) were classified as Category 3 by sponsors, split nearly evenly between Categories 3a and 3b. At least one DRA

concurred with the sponsor's proposal of Category 3a/3b in 24 cases (77% concordance). Three CADS (7%) were classified as Category 1 by sponsors. Sponsors concluded for the rest (26%) that a 2yr rat study would add value to the carcinogenicity assessment (i.e., Category 2). Not all Category 3a/b designations by DRAs were unanimous. Table 2 summarizes the degree of concordance among DRAs in concurring with Sponsors on designating Category 3A/B. Among these 24 CADs, the DRAs unanimously agreed with a Category 3a/b designation in 10 cases (~42%), and at least one DRA agreed in 14 cases (58%).

Table 1: Category designation by Sponsors and Drug Regulatory Agencies for Carcinogenicity Assessment Documents

	Sponsor	DRAs
Cat 1	3	2*
Cat 2	12	20**
Cat 3a/b	31	24
Total:	**46**	**46**

*Includes 1 case of split Cat 1/2 decision
**Includes 2 cases of split 1/2 or 2/3a decision

Table 2: Concordance among DRAs on Sponsor-proposed Category 3a/b designations.

DRA Category 3a/b Count	
Unanimous call	10
Split call	14
Split + Unanimous Call	**24**

Evaluation of the Concordance among DRA's in relation to time.

The number of DRAs contributing to the evaluation period has increased from three (EU, FDA, PMDA) to five (with Health Canada and Swissmedic). This increase can reduce the probability of achieving a unanimous decision. In Table 3 the periods have been divided per year or per participation by additional DRAs.

We expected that during the course of the prospective period there would be an increase in unanimity, because of the exchange of opinions, and discussion on issues that repeatedly were being used to change a Category 3 designation to Category 2. Looking at the decisions of individual DRA's, it is evident that some DRA's were more reluctant to give a Category 3, often expecting additional value from a 2-yr rat study, but this cannot be generalized to all DRA's. Furthermore, there are 4 cases over 2016 and 2017 where a designation of Category 3a/b was unanimously achieved by all 5 contributing DRAs. Further discussion is needed how to reach better concordance among the DRA's. In some cases, it is just a lack of information which led to designation of Category 2, instead of agreeing with a Category 3a or 3b. In the next section, specific examples illustrate the difficulties in assessing the category. Specifically,

the requirements for meeting a set of higher evidentiary standards for first-in-class compounds by sponsors seeking Category 3 are still difficult to define precisely.

Table 3. Scoring list of CAD's over the Prospective Evaluation Period 2014-2017

	2014		Till Oct 2015		Nov. 2015 and 2016		2017		Total	
Category	Sponsor	DRA (3)	Sponsor	DRA (4)	Sponsor	DRA (5)	Sponsor	DRA (5)	Sponsor	DRA
1 unan	-		1	-	2	1	-		3	1
1 split						1				1*
2 unan	1	2	4	3	2	2	2	2	9	9
2 split		4		5		7		6		22*
3A unan	2	1	6	4	4		4	1	16	6
3A split		2		2		5		3		12*
3B unan	5	1	1	-	5	1	5	2	16	4
3B split		1		-				3		4*
Total	8		12		13		11		44	

**Sponsors have proposed a single category for their compound. A split opinion was only possible for the DRA's. Therefore, total numbers are given only for sponsor-categories, as split decisions by the DRAs will lead to an increase. In 2014 Health Canada was an observer and, although present during teleconferences, did not contribute to the scoring. In 2015 HC became a member, while in November 2015 Swissmedic also became a member, and both contributed to the scoring at that time. Therefore, we combined the scoring from November 2015 with those from 2016. Two compounds (F10 and F22) were removed from the dataset, which explains the discrepancy with Table 1.*

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

As of May 2017, the DRAs received a total of 17 Summary Reports from completed 2yr rat studies. The DRAs had jointly discussed 14 of these 17 cases, among which 5 correspond to CADs designated Category 3a or 3b by both the Sponsor and the DRAs. The remaining 9 CADs were designated Category 2 by the DRAs (Table 4). The scope of the dataset adequately satisfied the threshold set forth in the Dec 2015 status update for an interim analysis that compares the CADs with the outcome of the completed 2yr rat studies. The interim analysis was, in part, intended to determine if the arguments that supported a Category 3a/b designation by DRAs and sponsors were in fact reasonably consistent with the actual 2yr rat study outcome. A study outcome starkly different from a Category 3a/b CAD designation would argue against the viability of the weight-of-evidence approach and against continuation of the prospective study as currently designed.

Table 4: CAD category designations of 14 reviewed studies**

CAD designation	Sponsor	DRAs
Category 2	4	9
Category 3a/b	10	5

** *As of December 2017 22 Summary Reports have been received.*

Harmonized Category 3a/b (DRAs concurred with Sponsor's designation)
The DRAs concurred with the Sponsor's CAD Category 3a/b designation in 5 of 10 cases, reflecting 50% concordance between the Sponsor and DRAs. Preliminarily, the 2yr rat study outcome for each of the 5 CADs appears consistent with the weight-of-evidence arguments in each corresponding CAD. In each case, the Sponsor and the DRAs agreed that the WOE presented in the CAD provided a sufficient basis for assessing carcinogenic risk without data from a 2yr rat bioassay and, in each case, either no drug-related tumors, or only anticipated human-irrelevant tumors were observed in the 2yr bioassay.

An issue of ongoing interest is whether a weight-of-evidence approach could be applied to first-in-class compounds, for which less is often known regarding the association of pharmacological effects with e.g. proliferative activity than for follow-on compounds of an established drug class. In general, a higher evidentiary standard is contemplated as necessary for supporting a WOE approach for first-in-class compounds (Status report 2015). As an example, 'Compound X' is a first-in-class inhibitor of a broadly expressed GPCR which was designated Category 3B by both the sponsor and the DRAs (harmonized Category 3). The higher evidentiary standard in this case was met by robust literature suggesting that inhibition of the pharmacological target would have anti-neoplastic properties, and by the absence of drug-related tumors from a 2yr rat study conducted with a similar drug not in clinical development (congener from the same company). These lines of evidence were in addition to a supportive toxicology, pharmacology, and genotoxicity profile for Compound X. Results of the 2yr rat bioassay with Compound X indicated an absence of drug-related tumors, consistent with the WOE assessment from the CAD. Non-neoplastic findings included vacuolation of the intestinal epithelia at all doses, a finding that was observed in the 6 month toxicology study and addressed in the WOE

assessment. Defining the type and scope of data necessary to provide a higher evidentiary standard for first-in-class compounds without being overly prescriptive will be one focus of the EWG's continued work.

Non-Harmonized Cat 3a/b (DRAs did not concur with Sponsor's designation)
The DRAs designated Category 2 for five CADs in which the Sponsor proposed Category 3a/b. In each case, either no drug-related tumors or anticipated human-irrelevant tumors were observed in the 2yr bioassay, generally consistent with the Sponsor's WOE assessment. Examination of the reasons why DRAs disagreed with the Sponsor's original designation revealed issues potentially addressable with additional data in some cases, whereas for others the conduct of a 2yr rat study was still considered necessary for an adequate assessment of carcinogenic risk.

Commonly, a lack of information rather than a definitive for-cause concern for carcinogenicity precluded the DRAs from arriving at a confident designation of Category 3. Insufficient metabolite qualification, insufficient characterization of immunomodulatory or hormonal signals, unexplained toxicity findings of potential neoplastic concern (e.g., hyperplasia, inflammation), and insufficient off-target screening were common deficiencies noted by DRAs. It is likely that such information could be obtained in a regulatory setting which could potentially support a different categorization by the reviewing DRA.

In other cases, attributes of the compound precluded, in the DRA's estimation, confident prediction of the 2yr rat study outcome or the carcinogenic risk to humans. For example, Compound Y is an inhibitor of multiple cellular kinases with weaker activity towards several off-target proteins. The literature suggests that inhibition of the intended kinases would be anti-proliferative, and that activity at off-target sites was not linked to tumor formation. Similar drugs approved in the class, but with differing target specificities from Compound Y, showed a mixed picture of drug-related tumors in one rat study, no tumors in another rat study, and tumors in a transgenic mouse study. A six-month study in RasH2 transgenic mice with Compound Y yielded no drug-related tumors. The Sponsor emphasized the anti-neoplastic potential of inhibiting the intended targets and the generally non-concerning toxicity profile of Compound Y in proposing Category 3b. In designating Category 2, the DRAs emphasized the differing target specificities and inconsistent tumor profile of compounds in the class, concluding that a 2yr rat study would in fact add value as a compound-specific assessment of carcinogenic risk for Compound Y. The results of the 2yr rat study with Compound Y showed an absence of drug-related tumors; non-neoplastic toxicities were generally consistent with target inhibition. While the tumor outcome did indeed prove consistent with the Sponsor's expectations, the DRAs considered the negative tumor outcome as important value added to the carcinogenic assessment for Compound Y in a drug class with variable pharmacology and an inconsistent rodent tumor profile.

As Category 3a/b would represent the primary potential change to the existing S1 guidelines, the EWG intends to focus on defining the critical WOE elements that contributed to a unanimous designation of Category 3a/b by the Sponsor and the DRAs, assuming that the

outcome of the associated 2yr rat studies continue to be consistent with the CADs. Focusing on those cases that gained unanimous Category 3 designation in the prospective study would ideally maximize regulatory harmonization in deciding when a WOE approach without data from a 2yr rat study would be an adequate assessment of an investigational drug's carcinogenic potential.

Category 2 Cases

Among the 14 cases reviewed by the EWG, three were unanimously designated Category 2 (2yr rat study required) by the Sponsor and DRAs. The EWG examined these cases to discern if the outcome of the 2yr rat study provided value as anticipated in the associated CAD. The study outcome indeed provided information considered valuable in two of the cases: in the first, a positive tumor outcome for a compound with complex pharmacology helped place risk within the existing drug class and addressed concerns for off-target and hormonal activity observed in the toxicology program; for the second, a negative tumor outcome addressed renal and adrenal lesions observed in the toxicology program for a compound considered first-in-class by the DRAs. The third compound presented a carcinogenic risk based on pharmacologic mode of action supported by proliferative lesions observed in the non-rodent and rodent toxicology studies. The Sponsor anticipated that a 2yr rat study would provide exposure-response information that would inform the level of carcinogenic risk; however, the compound was substantially less potent in rats than in humans. The 2yr rat study was negative for drug-induced tumors but showed pre-neoplastic lesions in target tissues. The substantial difference in potency between rats and humans confounds interpretation of exposure-response data for risk assessment and therefore the intended value of the study was not fully met in this case. It is feasible that alternative assessments could be considered in cases where the anticipated value of the 2yr rat study would not be reasonably achieved due to relevant differences in drug action between humans and rodents.

Final remark: No cases were identified where the results of the 2yr rat bioassay were clearly and meaningfully different from the prospective WOE assessment provided in the submitted CADs. The EWG concluded that these results of the interim analysis are sufficiently supportive to continue acceptance of final study reports and continue the evaluative period to a decisional analysis once the dataset reaches a minimum of 20 Category 3a/b cases.

References:

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