

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS
FOR PHARMACEUTICALS FOR HUMAN USE

The ICHS1 Regulatory Testing Paradigm of Carcinogenicity in rats - Status Report

Introduction

The ICH S1 Expert Working Group (EWG) convened in Jacksonville, Florida in December 2015 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 of actions taken by the EWG to ensure successful completion of the study.

Background: The RND hypothesis and the Prospective Evaluation Study

Based on retrospective analyses, the ICH S1 EWG hypothesized that a weight-of-evidence evaluation can, in certain cases, provide sufficient information to conclude that a given pharmaceutical presents a negligible risk or, conversely, a likely risk of human carcinogenicity without conducting a 2 year rat carcinogenicity study. A prospective evaluation study was considered necessary to address this hypothesis, which in case of confirmation, would inform the EWG on appropriate revisions to the ICH S1 Guideline. The RND posted to the ICH website in August 2013 thus announced the start of this prospective evaluation study, whereby sponsors voluntarily submit Carcinogenicity Assessment Documents (CADs). A CAD addresses the carcinogenic potential of an investigational pharmaceutical and predicts the outcome and value of the planned 2 year rat carcinogenicity study, and based on the level of certainty a company is expected to indicate the need for such a study or to claim a (virtual) waiver. Each participating Drug Regulatory Agency (DRA) independently reviews the submitted CADs and the rationale for concurrence or non-concurrence with the sponsor's proposal is documented. The predicted value and outcome of the 2 year rat study in the CADs are then checked against the actual value and outcome of the 2 year rat studies as they are completed and reported to the DRAs. Results on the accuracy of predictions and the degree of concordance among all parties are anticipated to help define the conditions under which a weight-of-evidence evaluation is an appropriate alternative to a 2 year rat carcinogenicity study. If this is the case then after revising the guideline, a waiver of a rat 2 year study might be granted by the DRA's.

State of the Prospective Evaluation Study (December 2015)

DRA Participation: The RND published in August 2013 listed the US FDA, the EMA, and the MHLW/PMDA as the participating DRAs in the prospective study. Since then, Health Canada joined in the spring of 2014 and Swissmedic in the fall of 2015 as active DRA participants. All five DRAs will participate fully in the prospective study consistent with processes described in the RND. Contact information for each DRA is listed in the 2015 RND revision.

Sponsor Participation and CAD Submissions: From August 2013 to September 2015, the DRAs received and reviewed 25 CADs at a rate of approximately 1 CAD per month. The number of CADs submitted accounts for approximately one-third the number of 2 year rat study protocols received by the FDA's Executive Carcinogenicity Assessment Committee during this period. In the interest of capturing as many cases as feasible, the 2013 RND allowed CADs to be authored within the first 18 months of an ongoing rat carcinogenicity study, but encouraged sponsors to author CADs within the first 12 months to further minimize potential bias. Among the 25 CADs received, 36% were authored in the first year of an ongoing 2 year rat study and 64% were authored in the second year. Among the CADs authored in the second year, 75% were written during months 17/18 of an ongoing rat study. Submission of 'second year' CADs has occurred throughout the 2 year collection period. As the prospective study now enters its third year, and in an effort to further reduce concerns of bias, the EWG agreed to restrict acceptance of CADs to only those authored within the first 14 months of an ongoing 2 year rat carcinogenicity study, effective June 1, 2016. This change is described in the 2015 RND revision.

CAD Categories and Concordance: The 25 CADs comprised diverse chemical classes and clinical indications, including several first-in-class compounds. Based on the reasoning in the CAD, 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 25 CADs submitted. A majority of Sponsors (64%) proposed category 3, split evenly between categories 3a and 3b. A designation of category 3a or 3b is a proposal that existing data is sufficient to characterize the carcinogenic risk of the compound without the need for a 2 year rat study. As category 3 compounds would represent the most notable departure from the current S1 guideline (waiving the need for the 2 year rat study), the 2013 RND anticipated that at least 20 category 3 cases, or $\geq 40\%$ of the targeted 50 CADs, would be necessary to address the viability of a weight-of-evidence option.

After review and discussion of each CAD, the DRAs concurred with the sponsor's proposal of a category 3a or 3b for 6 of the 16 cases (37% concordance). The DRAs did not concur with the sponsor's proposed category 3a/b in 7 cases, concluding instead that the compound should fall under category 2, and a 2 year rat study would have added value. For the remaining 3 category 3a/b cases proposed by sponsors, the DRAs could not reach consensus on a single category, resulting in only partial alignment for category 3a/b.

The DRAs concurred that category 2 (i.e., 2 year rat study would add value) was an appropriate designation for all 7 category 2 CADs submitted by sponsors.

Among the 2 CADs submitted by sponsors as category 1 (i.e., clear human risk, 2 year rat study unnecessary), the DRAs concurred in one case but concluded that a 2 year study could add value by defining the severity of the cancer risk for the other case, and therefore arrived at a category 2 designation.

Table 1: Category designation by Sponsors and Drug Regulatory Agencies for Carcinogenicity Assessment Documents submitted through December, 2015.

	Sponsor	DRAs
Category 1	2	1
Category 2	7	15
Category 3a	8	5
Category 3b	8	1
Partial DRA Alignment	0	3

Weight-of-Evidence Elements: In general, the content of submitted CADs addressed each of the weight-of-evidence elements described in Appendix 1 of the 2013 RND, as appropriate for each investigational pharmaceutical. Conclusions regarding the relative contribution and value of each weight-of-evidence criteria would be premature at this point in the study, as relatively few CADs have been received and comparison of predictions in the CADs to actual study outcomes has yet to occur. What follows, therefore, are general comments on primary factors that the DRAs have encountered in reviewing and categorizing CADs. These comments are intended to aid Sponsors in preparing CADs and selecting a category that is likely to achieve concurrence by the DRA S1 review committees. It should be taken into account that also the process of category designation by the DRA's is a learning process.

DRA-Sponsor concurrence on Category 3a/b: For these cases, the data for each weight-of-evidence element were complimentary in supporting little or no concern for carcinogenic potential of the compound. In particular, the pharmacology of the drug target was typically well-known and did not involve carcinogenic pathways, and relevant toxicology/hormonal findings (if present) in the chronic studies were adequately addressed and did not raise concern. Of note, each of the 6 cases included 'negative' results from one or more completed rodent carcinogenicity studies with other compounds in the same pharmacological class (from either published or unpublished studies). Screens for off-target activity, while notably variable in extent and robustness, did not reveal concerning pharmacological

interactions, and all compounds did not exhibit genotoxic activity as determined by batteries recommended in the ICH S2 Guideline.

DRA-Sponsor disagreement on Category 3a/b: Differences in categorization between sponsors and DRAs arose from differences in scientific opinion of the data presented and from various deficiencies in the CAD write-ups. Differences in scientific opinion arose on various aspects, including the relevance of toxicological or hormonal findings seen in the chronic studies, the implications of the pharmacological complexity or off-target activity of the compound, and the importance of prior experience with other compounds in the same or similar pharmacological class. The DRAs generally agreed that because prior class experience is absent for first-in-class compounds, a higher evidentiary standard would be needed to support a category 3a/b designation. These type of deficiencies, when noted in the CADs, prompted DRAs to choose category 2.

It is tempting to suggest that if such deficiencies were remedied, this may have resulted in a different categorization by the DRAs (or by the sponsor). For example, on occasion relevant literature was missing that either raised or reduced concern of carcinogenic potential; comparative exposure data for human metabolites was often missing; the relevance of concerning histological findings or hormonal perturbation in toxicology studies was occasionally not adequately addressed; assessment of target selectivity was often not well described; and potentially supportive information from non-rodent toxicology studies or from human exposures were not always addressed. In a few cases, such as with immunomodulators where rodent carcinogenicity studies might not be informative, alternative assessments that characterized the extent of immunomodulation or suppression by the compound was not well-addressed. Thus far the RND did not describe a procedure of interactions between the sponsor and the primary DRAs regarding potential deficiencies in the CAD.

Therefore, the EWG agreed in Jacksonville that in future cases where a DRA identifies specific 'missing' data considered pivotal for categorization, a single (i.e., one-time) information request may be sent to the submitting sponsor via the primary DRA that received the CAD. The sponsor could then decide whether to provide the requested information back to the primary DRA for further consideration. This change to the CAD review process is intended to increase concordance on categorizations between DRAs and sponsors and, in addition, among the DRAs themselves.

Disagreements on Category between DRAs: After independently reviewing and categorizing CADs, the DRAs met by teleconference to assess intra-DRA concordance and to seek alignment on a category. In three cases, only partial alignment was reached on a category. In each case, the sponsor proposed a category 3a or 3b, and the DRAs were split between category 3a/b and category 2. Indeed, in 2 of the 3 cases, individual DRAs reported only partial alignment within their own CAD review committees, underscoring the complexity occasionally encountered in applying a weight-of-evidence approach involving multiple relevant criteria. In various cases, a DRA would place greater weight than another on a given finding, particularly for hormonal effects of a compound, which would drive a difference in categorization. In other cases there is a difference between DRA's (or among internal committee members) about the impact of a compound being first-in class, as it is associated by definition with a high level of uncertainty. It is feasible that upon evaluation of the 2 year rat study outcomes, clarity may be gained on the weight-of-evidence criteria found to be most informative in the CADs. Together with

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the information requests described above and continued discussion among DRAs on the application of the weight-of-evidence criteria, discrepancies in categorization across the DRAs is expected to be minimal but not absent.

Rat Carcinogenicity Report Submission: Based on the start dates noted in the 25 submitted CADs and allowing for a 3 year period, results from the 2 year rat studies should be available by November 2017. As of December 2015, the DRAs have received but have not jointly reviewed 3 of 5 available study results. The results were submitted as executive summaries via the same process as the corresponding CADs; whether regulatory submission of the final study reports has occurred is not known. The submitted executive summaries have highlighted the importance of a comprehensive document complete with histopathology tables to allow the DRA's CAD review committees to draw conclusions prior to receipt of the regulatory submission. The EWG discussed the content and submission process for the 2 year rat studies at the 2015 ICH meeting in Florida. Results from that discussion are described in the 2015 RND revision (available at the ICH website) and a separate document that further describes the content and options for submission of the 2 year rat study will be sent to all sponsors that submit a CAD.

Actions taken by EWG to ensure successful study completion: The 2013 RND estimated that a 2 year collection period would be necessary to collect approximately 50 CADs with a substantial fraction of category 3a/b cases. Based on the actual rate of sponsor participation and CAD submissions, the EWG agreed to extend the period for CAD submissions by 2 years, to the end of December 2017. The EWG recognizes that alignment around category 3 CADs that are substantiated by results from 2 year rat studies are most important, as such cases may dictate the conditions under which a 2 year rat study waiver is feasible. Therefore, the EWG agreed that a decisional analysis would be appropriate when the dataset includes 20 category 3 cases (i.e., CAD + study report), irrespective of the total number of CAD cases received. For the purposes of reaching a decisional analysis in a timely manner, category 3 cases are defined as those CADs where at least one DRA concurs with the sponsor that a 2 year rat study waiver is appropriate. The EWG also agreed that an interim analysis should be conducted when the dataset includes ≥ 6 category 3 cases and ≥ 10 category 2 cases. The decisional analysis is intended to define the scope of potential modification to S1 Guidelines. The extension of the period for CAD submissions will result in a corresponding delay in the collection of study reports as well.

This 2 year extension to the prospective study is expected to allow for the interim analysis to occur near November 2016 and a decisional analysis with ≥ 20 CAD cases to occur by the end of 2019. The set of data as defined above is necessary for the EWG to move forward in this process; however, participation by Sponsors in submitting CADs is lower than expected, necessitating extension of the study. In the US, a reminder of the S1 EWG's work has been included in the minutes to the Sponsor from the FDA's Executive Carcinogenicity Assessment Committee to encourage greater participation. The DRA members of the EWG continue to encourage those pharmaceutical companies that have not contributed to this study to reconsider and do so. This study serves as a learning process for both Sponsors and DRAs, and is considered a critical component in addressing the viability of a weight of evidence approach to carcinogenicity assessment of pharmaceuticals, which holds potential benefit to both the public and to industry.