Revised 22 January 2016

# Proposed Change to Rodent Carcinogenicity Testing of Pharmaceuticals - Regulatory Notice Document

## Summary


A change to the current ICH S1 guidance on rodent carcinogenicity testing is being considered. The goal of this potential change is to introduce a more comprehensive and integrated approach to address the risk of human carcinogenicity of small molecule pharmaceuticals, and to define conditions under which 2-yr rat carcinogenicity studies add value to that assessment. This effort is not applicable to biotechnology-derived pharmaceuticals that follow the ICH S6(R1) guidance document.

Datasets evaluated by the ICH S1 expert working group (S1 EWG) suggest that knowledge of pharmacologic targets and pathways together with toxicological and other data can, in certain cases, provide sufficient information to anticipate the outcome of 2-yr rat carcinogenicity studies and their potential value in predicting the risk of human carcinogenicity of a given pharmaceutical. Consideration of this information is hypothesized to provide sufficient information to conclude that a given pharmaceutical in certain cases presents a negligible risk or, conversely, a likely risk of human carcinogenicity without conducting a 2-yr rat carcinogenicity study. It is envisioned that Sponsors of such pharmaceuticals would provide Drug Regulatory Agencies (DRAs) a Carcinogenicity Assessment Document (CAD) which could justify a 'waiver request' that seeks to omit the conduct of 2-yr rat carcinogenicity studies. The CAD would address the overall carcinogenic risk of the investigational drug as predicted by the endpoints discussed in this document and a rationale for why the conduct of 2-yr rat carcinogenicity studies would or would not add value to that assessment.

Prospective evaluation of this proposed hypothesis is necessary to justify proceeding with revision of the ICH S1 guidance. A prospective evaluation period is sought wherein Sponsors will be strongly encouraged to submit CADs to DRAs for all investigational pharmaceuticals with ongoing or planned 2-yr rat carcinogenicity studies. DRAs from each region will independently review the submitted assessments to evaluate the degree of concordance with Sponsors and between regulatory regions. During this prospective evaluation period the waiver requests are not to be granted but are intended solely for gathering experience and hypothesis testing (see below, however, for existing waiver capability under current S1A Guidance). Submitted CADs will be compared to the outcome of the 2-yr rat carcinogenicity studies to evaluate the accuracy of the predictions to the actual experimental results. Experience from this prospective evaluation period is considered critical to informing the S1 EWG's efforts in revising the current paradigm of assessing the carcinogenicity of small molecules as described in ICH S1 guidance.

# Introduction

## Statement of the problem

The strategy of testing for carcinogenic potential was the first safety topic of ICH when this process started. The main topics were the need to conduct a study (S1A), the selection criteria for the rodent species (S1B) and the criteria for dose selection (S1C (R2)). During the discussion in that period the relevance of the life-time carcinogenicity studies in rats and mice was already highly debated, but in the absence of an alternative the outcome of the negotiations did not really change the basic strategy of testing pharmaceuticals for human use in two rodent species. A proposal to delete the mouse as a second species did not receive sufficient support, although it paved the way to introduce transgenic mice with a 6-9 months treatment as an appropriate alternative (S1B).

In the following years considerable resources have been spent to evaluate the approaches using the transgenic mice (Pritchard et al., 2003; Cohen et al., 2001). Also other models and approaches received attention, especially whether the outcome of carcinogenicity studies could be predicted on the basis of the results of 3-month or 6-month studies (Cohen, 2004; Jacobs, 2005).

In this framework, researchers from a US-based company started a project with 60 company-owned and marketed compounds (Reddy et al., 2010) with the outcome that a negative histopathology result in rats (e.g., no evidence of hyperplasia in any organ) might be predictive for the absence of tumors in a 2-yr rat carcinogenicity study. This led to the conduct of a much broader project involving 13 companies as described below.

## Historical Background

The conclusions from this PhRMA analysis of a dataset containing 182 compounds (Sistare et al., 2011) were consistent with the conclusions of the earlier paper. Based on this analysis it was concluded that negative histopathology in a chronic rat study, together with a negative result in genotoxicity and negative evidence of a hormonal mechanism, could predict with 82% accuracy a negative outcome of the 2-yr rat carcinogenicity study for these compounds. This could apply to around 30-40% of the compounds.

In the discussion of these results with the DRAs, a question was raised regarding the impact of the pharmacological properties of the compounds first for the false negative compounds, but with consequences for all compounds. The EU DRA delegation has conducted an analysis and concluded that pharmacodynamic activity was responsible for a majority of the tumor-inducing compounds. In addition several compounds associated with hepatocellular hypertrophy or liver

enzyme induction were prone to induce tumors in thyroid and testes, and not always in liver.

In addition to the PhRMA dataset analysis, the FDA conducted a similar study with 44 unique compounds, and the JPMA conducted a study with 64 compounds with minimal overlap of either dataset. These analyses confirmed the earlier conclusions from the PhRMA dataset with respect to negative predictivity, as well as the EU DRA delegation conclusions regarding the relation with the pharmacology. In the initial discussion on the relevance of rats and mice in the process coming to ICH S1B, both Europe (van Oosterhout, et al., 1997) and US (Contrera, et al., 1997) have published a dataset of several hundreds of compounds with life-time carcinogenicity studies in rats and mice. The EU DRA delegation has used the background data from these publications relating the pharmacology of the compounds and the outcome of the rat carcinogenicity studies. This analysis fully confirmed the conclusions reached earlier on the PhRMA database.

**Conclusions from analyses conducted**

From the retrospective analysis of the various datasets (PhRMA, FDA, JPMA, and EU + FDA) it was concluded that based on pharmacology, genotoxicity, and chronic toxicity data (usually present at the end of phase 2 in the development of a new pharmaceutical) the outcome of the 2-yr rat carcinogenicity study can be predicted with reasonable assurance at the two extremes of the spectrum. Negative predictions can be made when predictive carcinogenic signals are absent and positive predictions can be made when such signals are present. In between a category of compounds still remain for which the outcome of the carcinogenicity studies cannot be predicted with sufficient certainty.

## Proposal

The processes initiated by this proposal are expected to improve pharmaceutical carcinogenicity evaluations, reduce use of animals in accordance with the 3Rs (reduce/refine/replace) principles, reduce the use of drug development resources, and reduce timelines to market authorization in some cases, all without compromise to patient safety. Analyses of the data sets described above, suggest that a carcinogenicity assessment could be completed for certain pharmaceuticals without conducting a 2-yr rat carcinogenicity study. From these databases it can be shown that pharmacologic and toxicologic data from numerous sources including toxicology studies of 6-month duration can be integrated to predict with sufficient certainty that a given pharmaceutical will fall into one of 3 main categories: Category 1 - highly likely to be tumorigenic in humans such that a product would be labeled accordingly and 2-yr rat, 2-yr mouse, or transgenic mouse carcinogenicity studies would not add value. Category 2 - the available sets of pharmacologic and toxicologic data indicate that tumorigenic potential for humans is uncertain and rodent carcinogenicity studies are likely to add value to

human risk assessment. Accordingly, current S1B Guidance describes options for rodent carcinogenicity testing. Category 3a - highly likely to be tumorigenic in rats but not in humans through prior established and well recognized mechanisms known to be human irrelevant, such that a 2-yr rat study would not add value; or Category 3b - highly likely not to be tumorigenic in both rats or humans such that no 2-yr rat study is needed. A study in a transgenic mouse could prove useful for justifying a Category 3 assignment. It is envisioned that in the absence of such data either a 2-yr mouse or a transgenic mouse carcinogenicity study would be needed in most cases.

A set of WOE (Appendix 1) factors has been developed. During the prospective evaluation period Sponsors are encouraged to apply the available WOE for each pharmaceutical prior to 2-yr rat carcinogenicity study completion and to assign a pharmaceutical candidate to Category 1, 2, 3a or 3b in a CAD with respect to the expected value and need for 2-yr rat carcinogenicity testing. Sponsors are encouraged to submit the CAD to the DRAs explaining and justifying their position that a waiver decision is, or is not, appropriate for each pharmaceutical prior to knowing the outcome of carcinogenicity testing.

## Scope and Process for a Prospective Evaluation Period

**Objective**

The intent of the prospective evaluation period is to gain experience and generate data that address critical aspects of proposed changes to ICH S1 guidance that could not be answered by retrospective analysis of the existing datasets. Specifically, these critical aspects include how well the WOE described herein will predict the outcome and value of 2-yr rat carcinogenicity study results, and how often the DRAs are in accordance with Sponsors and with each other regarding the need to conduct a 2-yr rat carcinogenicity study based on the arguments put forth in CADs.

This effort is not applicable to biotechnology-derived pharmaceuticals that follow the ICH S6(R1) guidance document.

Sponsors are encouraged, to submit CADs for *all* investigational pharmaceuticals subject to 2-yr rat carcinogenicity studies under current ICH S1A Guideline as well as for those with ongoing 2-yr rat carcinogenicity studies. It is encouraged that CADs be authored prior to or within the first 12 months of initiation of dosing. Although the initial RND allowed submission of CADs for ongoing rat carcinogenicity studies not exceeding 18 months, it was decided to reduce the acceptable in-life phase to 14 months for all CAD submissions effective June 1, 2016 in order to further minimize bias. CAD submissions received after this date for studies that are beyond 14 months duration will no longer be accepted. The date that the document was authored should be specified in the CAD in relation to the start of drug administration. The results of the prospective evaluation period

will inform future revisions to the ICH S1 guidance. CADs submitted under the prospective evaluation period are not considered regulatory documents or a substitute for the standard carcinogenicity assessment.

Based on analyses of the number of rodent carcinogenicity study reports received by DRAs since 2010, it was estimated that a two-year data collection period would be needed to reach a goal of evaluating CADs with 2-yr rat carcinogenicity data for fifty compounds. However given the frequency that CAD submissions are actually being submitted, this prospective evaluation period will be extended for an estimated additional 2 years. Broad and comprehensive participation by pharmaceutical companies in submitting CADs to DRAs for review is very critical for the success of this effort, to minimize bias, and to ensure completion within this extended evaluation period. Submission of CADs for all categorical designations is encouraged; however, submission of Category 3 compounds is of particular interest to the DRAs and critical to the success of this prospective evaluation, as these compounds would represent the most notable departure from current guidance (omitting 2-yr rat carcinogenicity study). Based on current data sets at least 20 Category 3 CADs (approximately 40% of compounds undergoing carcinogenicity testing based on the retrospective analyses) are needed to gain sufficient experience for potential guidance revision. Public notification that the prospective evaluation period has closed will be made to the ICH Website.

The 2-yr carcinogenicity study in the rat is the focus of this prospective evaluation period and is not intended to evaluate the mouse carcinogenicity study. A carcinogenicity study in a second rodent species would still be required for Category 3 compounds according to S1B Guidance.

For most compounds the rat is chosen as the primary rodent species for toxicity testing, but the mouse may be more appropriate and used for some compounds. An evaluation of the predictive nature of such mouse toxicology data has not been attempted and so its value for predicting the outcome of mouse carcinogenicity studies is not known and is therefore not in scope of this prospective evaluation period.

**Content of Submitted CADs**

Submissions should assess the carcinogenic potential for the investigational pharmaceutical under study, guided by the WOE approach described in Appendix 1. The CAD should address each factor considered pertinent to carcinogenic potential and not provide a general summary of the nonclinical profile of the pharmaceutical. Not all factors in Appendix 1 are expected to be applicable or available in all cases.

In addition to addressing the WOE in Appendix 1, the CAD should include the following critical elements (see Appendix 2):

1. Prediction of the actual tumor outcome from the planned/ongoing 2-yr rat carcinogenicity study (positive/tumor target organs, or absence of tumors)
2. Projected value of the anticipated 2-yr rat carcinogenicity study outcome to the overall carcinogenicity assessment and human risk implications
3. Categorical assignment with explicit statement and explanation as to whether the CAD supports: 1) conducting the 2-yr rat carcinogenicity study, or 2) a waiver request from conducting the 2-yr rat carcinogenicity study (or any carcinogenicity studies for Category 1 compounds).

The intent of the prospective evaluation period is to generate data relevant to future changes to ICH S1 guidance. As such, submitted CADs will have no impact on the drug development program in any region. Actual waivers of 2-yr rat carcinogenicity studies will not be granted, nor will CADs be used to support regulatory actions on development programs. Assessment of carcinogenicity during this period, and the need for lifetime studies in rodents, should follow existing ICH S1A guidance. Under the current S1A guidance, carcinogenicity testing for certain compounds is not warranted, such as in cases of unequivocally genotoxic compounds.

**Process of Submitting CADs**

Electronic CADs are requested for *all* investigational pharmaceuticals subject to a 2-yr rat carcinogenicity study under current ICH S1 guidance as well as for those with ongoing rat carcinogenicity studies, provided that dosing has not exceeded 14-month duration (effective as of June 1, 2016). A CAD Review Committee will be established in each DRA, and CAD reviewers will be separate from primary reviewers of the Sponsor's actual product file study data. Sponsors are requested to submit an anonymous electronic CAD with identifying cover letter, to one DRA (see addresses below) in the region where clinical trials are being conducted. That primary DRA's CAD secretariat will remove the cover letter with the Sponsor and product identity, add a code, share, and track only the anonymous electronic CAD with the CAD Review Committee and the other DRAs. Each DRA's CAD Review Committee will complete their evaluation based solely on the content of the coded anonymous CADs. All CAD Review Committees will therefore be blinded to Sponsor and compound identity. Only the primary contact DRA secretariat will have the capability of linking the CAD to the original submitting Sponsor.

Feedback will be provided promptly to the Sponsor relating to general adequacy of the CAD for review from the primary contact DRA through the secretariat. Based on current experience there were instances after discussion among all DRAs where further information or clarification would have been helpful to decide on the proposed category. Therefore going forward the primary DRA may request this from the sponsor before completing an evaluation of the CAD. If requested by the Sponsor, categorization of the CAD by each DRA's CAD Review Committee will be provided in a timely manner and prior to the Sponsor submitting the 2-yr rat carcinogenicity study results. Additional feedback

summarizing the scientific review of the CADs may be provided confidentially to Sponsors, if requested, only upon completion of the prospective evaluation period.

**Process of Submitting Rat Carcinogenicity Study Results**

Sponsors are to submit the 2-yr rat carcinogenicity study reports to the appropriate DRA according to current regional regulatory guidelines. Regulatory review of the carcinogenicity study will follow current regional practices. Review of the CADs as anonymous documents will preclude any potential bias in situations where a member of the CAD review committee may also be involved in scientific discussions of the 2-yr study report. Sponsors should send a notification email to the secretariat of the same DRA's CAD Review Committee (see addresses below) that the regulatory submission of the rat carcinogenicity study report has occurred, along with an electronic executive summary that the sponsor may choose to anonymize or not. It is also acceptable to submit an executive summary to the CAD secretariat prior to the regulatory submission of the study report. The executive summary should be comprehensive and include sufficient information to enable independent assessment of tumor outcome. In addition to the executive summary sponsors should submit tumor incidence tables including statistical analyses. Sponsors will receive further guidance regarding the submission process and content of executive summaries from the primary DRA upon receipt of the CAD. DRAs that do not receive the 2-yr rat carcinogenicity study report will be sent the Sponsor's executive summary. In reviewing the executive summary the DRAs will be blinded to its corresponding CAD by the secretariat of the primary DRA's CAD Review Committee.

In cases where the filing of the marketing application occurs at a date much later than the completion of the 2 yr rat study, Sponsors are encouraged to submit the study reports to the regulatory filing when available, to facilitate completion of the prospective evaluation period. For terminated programs, sponsors can submit the study report or an executive summary, following the process as described above.

**Evaluation of CADs and Study Results**

DRAs will convene only periodically but prior to receipt of 2-yr rat carcinogenicity study results to assess the concordance in categorizations between DRAs and Sponsors, and among DRAs. Efforts will be made during those meetings to seek alignment among DRAs and the results of those alignment efforts will be noted. During these meetings DRAs will remain blinded to the identity of both the compound and the Sponsor.

CADs will again be evaluated according to each of the following 3 points after receiving results of the regulatory review of the corresponding 2-yr rat study. The CADs will be evaluated based on the following attributes:

1. Accuracy of the prediction compared to the 2-yr rat carcinogenicity study tumor outcome using the WOE described herein.

2. Accuracy of the Sponsor's and the DRAs' original categorical assignments relative to actual overall study outcome.
3. Regulatory impact when the predicted tumor outcome may differ from the actual tumor outcome, influencing human health risk.

Emphasis on evaluation will be placed on attribute 3 above to minimize safety concerns by incorrect classifications of compounds to Category 3.

The DRAs will maintain product confidentiality in conducting independent analyses of the above attributes as well as compound identity. The proportion of compound categorization (1, 2, 3a, 3b) and the extent of Sponsor participation will be periodically reviewed with the ICH S1 EWG. Final results of the prospective evaluation period will be reviewed by the S1 EWG to inform revision of the current ICH S1 guidance. Publication in a peer-reviewed toxicologic journal of the prospective evaluation period experience and conclusions is planned.

**DRA Contact Information for Submission of CADs and Summary Study Reports**

CADs and final summary study reports, when applicable, should be submitted to the appropriate contact DRA as described above and listed below.

EMA: EMA-CAD@ema.europa.eu

FDA: FDA-CAD@fda.hhs.gov

PMDA: PMDA-CAD@pmda.go.jp

HC: HC-CAD@hc-sc.gc.ca

Swissmedic: SMC-CAD@swissmedic.ch

NOTE: It is recognized that two year rat studies can provide toxicology information in addition to neoplastic responses which would be missed in cases where a 2-yr rat carcinogenicity study is waived. However, this document and the prospective evaluation period are focused on addressing the need for 2-yr rat carcinogenicity studies based solely on anticipated tumor findings. A review of non-neoplastic lesions appearing uniquely in a 2-yr rat carcinogenicity study have been discussed and evaluated and found not to limit this weight-of-evidence approach to waiving the conduct of 2-yr rat carcinogenicity studies.

***References***

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Reddy MV, Sistare FD, Christensen JS, DeLuca JG, Wollenberg GK, DeGeorge JJ. (2010) An Evaluation of Chronic 6- and 12-Month Rat Toxicology Studies as Predictors of 2-Year Tumor Outcome. Vet Pathol 47, 614 – 629.

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Van Oosterhout JPJ, Van der Laan JW, De Waal EJ, Olejniczak K, Hilgenfeld M, Schmidt V, Bass R. (1997) The utility of Two Rodent species in Carcinogenic Risk Assessment of Pharmaceuticals in Europe. Regulatory Toxicology and Pharmacology 25, 6-17.

## Appendix 1. Weight-of-Evidence Factors for Consideration in a Carcinogenicity Assessment Document

Each of the factors listed below should be considered in formulating a prediction in the outcome and value of conducting a 2-yr rat carcinogenicity study and an overall integrated assessment of the carcinogenic risk for humans. Some factors can be appropriate for both, others more appropriate for one or the other purpose. This appendix can be used as a guide by Sponsors for writing a CAD.

- **Knowledge of intended drug target and pathway pharmacology, secondary pharmacology, & drug target distribution in rats and humans.**

  Target and pathway related mechanistic/pharmacologic and understood secondary pharmacologic characteristics can contribute to the prediction of outcomes of carcinogenicity studies, and can improve prediction of potential human carcinogens. The CAD is expected to convey a thorough and critical assessment of the Sponsor's knowledge of all such characteristics including a comprehensive literature review specifically addressing carcinogenicity risk. Examples of such data sources include the following:
  - Prior experience with other molecules in the drug class
  - Experience with human genetic polymorphisms in the target or pathway
  - Clinical trial data
  - Genetically engineered rodent models
  - Animal disease models
  - Unintended pharmacology
  - Hormonal perturbation
  - Targeted tissue genomic biomarker measurements

- **Genetic Toxicology Study Results**

  The criteria in ICH S2(R1) will be used to evaluate genetic toxicology data using a weight-of-evidence approach.

- **Histopathologic Evaluation of Repeated Dose Rat Toxicology Studies**

  Histopathologic risk factors of neoplasia should be evaluated in the 6-month chronic rat study. Findings seen only in shorter term repeated dose rat toxicity studies are generally considered of less value for 2-yr rat study outcome prediction, but should be addressed. Histopathologic findings of particular interest include cellular hypertrophy, diffuse and/or focal cellular hyperplasia, persistent tissue injury and/or chronic inflammation, preneoplastic changes, and tumors. It is important to address the human relevance of such findings. For example, liver tumors are observed at relatively high frequency in the rat, sometimes with Leydig cell and thyroid follicular cell tumors. Hepatocellular hypertrophy associated with increased liver weight often results from hepatic enzyme induction, the latter being a well understood mechanism of rodent specific tumorigenesis at these sites with little relevance to humans (McClain, 1989; Cook et al., 1999). The CAD should review the data supporting such mechanisms in assessing the risk for humans.

- **Exposure Margins in Chronic Rat Toxicology Studies**

  A high exposure margin in a chronic rat toxicology study absent of any carcinogenic risk factors can provide additional support for a carcinogenicity study waiver. Additionally, risk factors for neoplasia occurring only at high multiples of anticipated human exposure may provide additional support for considering a carcinogenicity study waiver. The inability to achieve high exposure margins in a chronic rat toxicology study due to limitations of tolerability, pharmacology, or absorption, would not preclude a rat carcinogenicity study waiver.

- Metabolic Profile

  As per ICH S1C(R2), a comparison of the metabolic profile between rats and humans should also be taken into account when assessing the potential carcinogenicity of small molecules. Therefore, the adequacy of the metabolic profile in rats and exposure to human metabolites should also be discussed in the CAD.

- **Evidence of Hormonal Perturbation**

  Evidence of hormonal perturbation should be considered from both repeated-dose and reproductive toxicology studies. Such evidence can come from weight, gross and/or microscopic changes in endocrine organs or parameters from reproductive toxicology studies. Serum hormone levels can be useful to address findings but are not always essential.

- **Immune Suppression**

  Immunosuppression can be a causative factor for tumorigenesis in humans. Effects on the immune system can alter tumor surveillance or result in tumors secondary to recrudescence of oncogenic viruses. As such, an assessment of potential impact to the immune system should be evaluated according to the ICH S8 guideline and factored into the CAD.

- **Special Studies and Endpoints**

  Data from special stains, new biomarkers, emerging technologies, and alternative test systems can be submitted with scientific rationale to help explain or predict animal and/or human carcinogenic pathways and mechanisms when they would contribute meaningfully.

- **Results of Non-Rodent Chronic Study**

  Assessment of carcinogenic risk factors in the non-rodent toxicology studies should be considered for human risk assessment regardless of results in the chronic rat study.

- **Transgenic Mouse Study**

  A transgenic mouse carcinogenicity study (usually rasH2 or p53+/- mouse) is not required for the WOE argument. However, if conducted on a case-by-case basis, a transgenic mouse carcinogenicity study can contribute to the WOE.

## Appendix 2: Template for Use in Submitting Carcinogenicity Assessment Documents

Check one: 1) ___ Sponsor DOES wish to receive DRA feedback.
2) ___ Sponsor DOES NOT wish to receive DRA feedback.

<table>
<tr><td colspan="3">Directions to Sponsor: Complete the left-side column for prediction of rat tumor outcome, value to overall carcinogenicity assessment and human risk implications, and categorical assignment/waiver request. The reviewing DRA will complete the 'DRA Concurrence' cell after review of the CAD, and will complete the right-side column after review of the 2yr rat carcinogenicity study report.</td></tr>
<tr><td colspan="3">Tumor Outcome from 2yr Rat Carcinogenicity Study</td></tr>
<tr><td rowspan="2">Prediction by Sponsor<br>(positive/negative; and target organs)<br>(consider "uncertain prediction" only for Category 2)</td><td colspan="2">Actual Outcome According to Sponsor<br>(positive/negative; and target organs)</td></tr>
<tr><td colspan="2">Actual Outcome According to DRA<br>(positive/negative; and target organs)</td></tr>
<tr><td colspan="3">Value to carcinogenicity assessment and human risk implications</td></tr>
<tr><td>Projected Value</td><td colspan="2">Actual Value</td></tr>
<tr><td colspan="3">Categorical Assignment and Waiver Request</td></tr>
<tr><td>Predicted Category by Sponsor</td><td>DRA Concurrence (Y/N) Predicted Category</td><td>Actual Category</td></tr>
<tr><td>Waiver requested (Y/N)</td><td>Waiver supported (Y/N)</td><td>Waiver supported (Y/N)</td></tr>
</table>