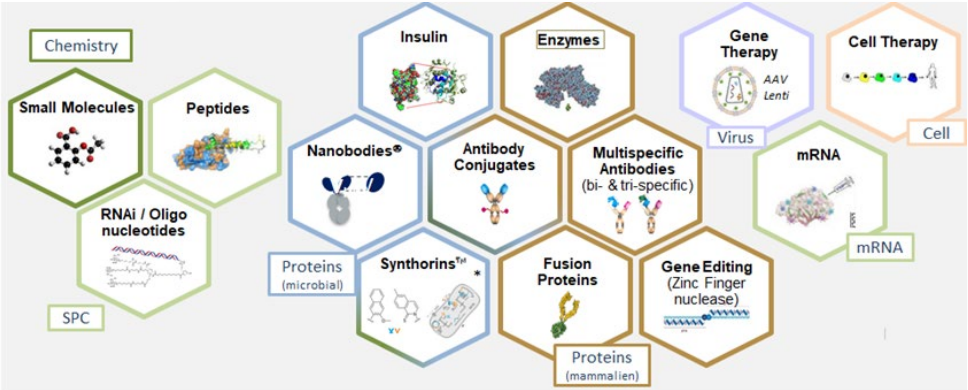

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Révision de la ligne directrice ICH-S1: un changement de paradigme ?

Philippe Detilleux, Global Head, Preclinical Safety, Sanofi R&D

The ICH-S1 Guidelines

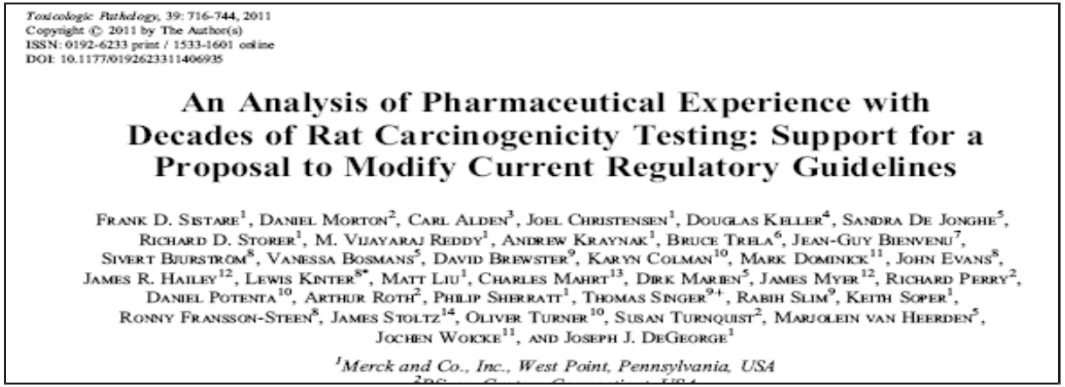
ICH-S1A:	**Guideline on the Need for Carcinogenicity Studies for Pharmaceuticals** (adopted 1995)
ICH-S1B:	**Testing for Carcinogenicity of Pharmaceuticals** (adopted 1997)
ICH-S1C(R2):	**Dose Selection for Carcinogenicity Studies** (adopted 1994, revised 2005 & 2008)

Many publications have questioned the value of current 2-year rodent testing practices

- **Reddy, et al., An Evaluation of Chronic 6- and 12-Month Rat Toxicology Studies as Predictors of 2-Year Tumor Outcome. Vet Pathol 2010.**
  - Chronic rat study is a good predictor of negative outcome in 2-yr rat
- **Alden, et al., A Critical Review of the Effectiveness of Pharmaceutical Carcinogenesis Testing in Predicting for Human Risk. Veterinary Pathology, 2011.**
  - 533 distinct cmpds available in PDR. 78 labeled w special warnings
  - 287 run in rodent carc assays (246 not evaluated).
  - (161/287) 56% tested positive BUT only (32/161) 20% had a special label warning – all others, human relevance uncertain, overall value/credibility of testing questioned…
- **Friedrich and Olejniczak, Evaluation of Carcinogenicity Studies of Medicinal Products for Human Use Authorised by the European Centralised Procedure (1995-2009) Regulatory Toxicology and Pharmacology, 2011**
  - (94/144) 65% cmpds tested positive, but only (11/94) 11% considered to hold human relevance

Conclusions from the PhRMA Carcinogenicity Database

Analysis Project – published Feb 2011



Toxicologic Pathology, 39: 716-744, 2011

ISSN: 0192-6233 print / 1533-1601 online
DOI: 10.1177/0192623311406935

An Analysis of Pharmaceutical Experience with Decades of Rat Carcinogenicity Testing: Support for a Proposal to Modify Current Regulatory Guidelines

Frank D. Sistare[1], Daniel Morton[2], Carl Alden[3], Joel Christensen[1], Douglas Keller[4], Sandra De Jonghe[5], Richard D. Storer[1], M. Vijayaraj Reddy[1], Andrew Kraynak[1], Bruce Triela[6], Jean-Guy Bienvenu[7], Sivert Bjurstrom[8], Vanessa Bosmans[5], David Brewster[9], Karyn Colman[10], Mark Dominick[11], John Evans[8], James R. Hailey[12], Lewis Kinter[8*], Matt Liu[1], Charles Mahrt[13], Dirk Marien[5], James Myer[12], Richard Perry[2], Daniel Potenta[10], Arthur Roth[2], Philip Sherratt[1], Thomas Singer[9+], Rabih Slim[9], Keith Soper[1], Ronny Fransson-Steen[8], James Stoltz[14], Oliver Turner[10], Susan Turnquist[2], Marjolein van Heerden[5], Jochen Wokke[11], and Joseph J. DeGeorge[1]

[1]*Merck and Co., Inc., West Point, Pennsylvania, USA*

- **Results of 190 pharmaceutical compounds and 76 IARC human carcinogenic chemicals = 266 total chemicals**
- **NO histologic risk factors for neoplasia in a 6-month rat study + NO genetic toxicology + NO hormonal perturbation signals = NO value added from conducting a 2-yr rat carco study.**
- **The results of these analyses launched discussions to modify current ICH carcinogenicity testing guidelines, while maintaining patient safety, accelerating patient access, and predicting elimination of approximately 40% of 2-yr rat carcinogenicity testing**

Steps taken subsequently toward ICH S1 Guidance Revision

- **FDA launched a separate and independent pilot data review and similar results seen with 44 new compounds, but interpretation on the applicability of the approach differed from that of PhRMA**
- **JPMA shared data mining results on an independent set of 64 compounds and again, similar results were seen.**
- **EMA completed unblinded analyses of all PhRMA, FDA, JPMA data, highlighting the added value of knowledge of on and off- target pharmacology, pathways, common class effects to carc outcome prediction, e.g., Liver enzyme inducers; dopamine blockers; beta agonists; PPARs**
- **ICH Steering Committee accepted to form an ICH EWG to consider revision of S1 ICH Guidance and a Regulatory Notice Document (RND) was Posted to ICH Website in Aug 2013 launching the Prospective Evaluation**

Dated 8 August 2013

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.

Objectives of the Prospective Study Period

- **Address critical aspects not addressed by retrospective study of existing data, particularly the consideration of pharmacology involvement**
- **Unbiased prospective evaluation as to how well the WOE (Weight of Evidence) elements predict the 2-yr rat carcinogenicity outcome**
- **How often Drug Regulatory Agencies (DRAs) are in agreement with sponsors and with each other based on arguments in the Carcinogenicity Assessment Document (CAD)**
- **Understand ability to predict with a high degree of certainty when the results of rat carcinogenicity studies do not add value and could justifiably be waived**

Regulatory Notice Document calls for sponsors to assign a CAD category based on WOE

Category 1: Highly Likely to be tumorigenic in humans. Label as such. A 2-year rat or 2-year mouse or transgenic mouse study would **not** add value.

Category 2: Tumorigenic potential for humans is uncertain. Rodent carco studies **likely to** add value to human risk assessment.

Category 3a: Highly likely tumorigenic to rats but not humans from prior known mechanisms irrelevant to humans. A 2-yr rat study would **not** add value.

Category 3b: High likely NOT to be tumorigenic to both rats and humans. A 2-yr rat study would **not** add value.

NOTE THAT for Category 3a & 3b the RND proposes a mouse carco study be conducted even when no 2 yr rat study – it is likely that the frequency of transgenic mouse study deployment frequency will grow

Overall Prospective Study Design

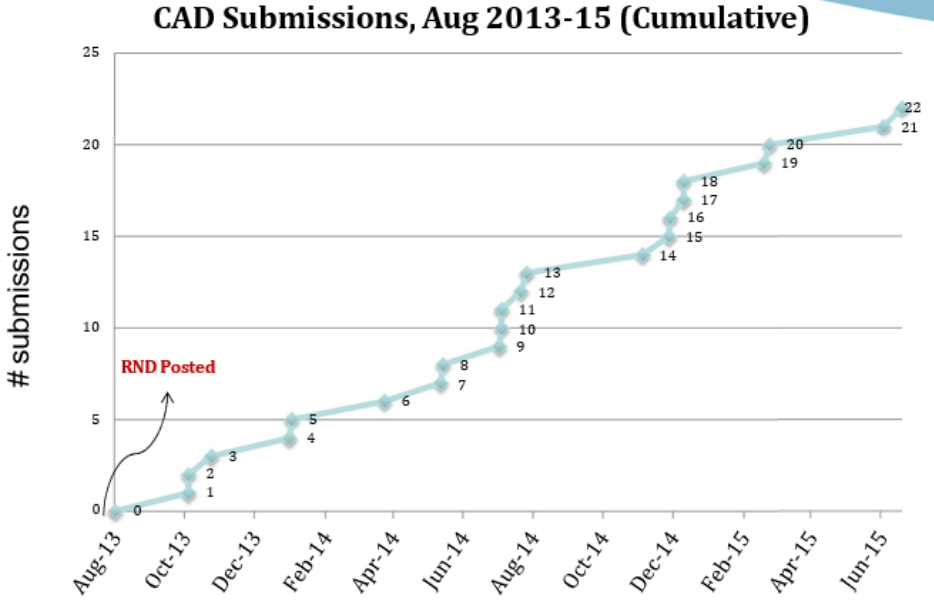
- **Part 1**
  - Sponsors of pharmaceuticals provide DRAs a blinded/anonymized CAD to justify a waiver (or no waiver) to conduct a 2-yr rat carco study
  - CAD addresses overall carcinogenicity risk based on the WOE endpoints and a rationale why 2-yr rat carco study would add or not add value
  - Analogous to ICH S6 Guidance for Biopharmaceutical Carcinogenicity Assessment
  - FDA/EMA/PMDA/HC share and independently evaluate blinded CADs
  - The DRA CAD Review Committee members are independent and insulated from DRA product reviewers
  - Predictions are locked in by sponsors prior to completion of month 18 of a 2-yr rat carco study and degree of concordance with sponsors and among DRAs are evaluated
- **Part 2**
  - Sponsor submits 2-yr rat carco study outcome to product Review Division and a blinded summary to the CAD Review Committee
  - DRA reviews results for the accuracy of CAD prediction
- **Overall :**
  - Two-year CAD collection period for 50 studies was expected with broad and comprehensive participation by pharmaceutical companies to minimize bias
  - Results of this prospective analysis are critical to consider revision of ICH S1 guidance to allow a potential waiver of a 2-yr rat study.

An Industry (IQ) and FDA update on ICH S1 Carcinogenicity Assessment Documents (CADS)

September 2015 Webinar

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Participation



✓ **11 sponsors submitted 18 CADs to FDA (as primary DRA)**

Prospective study extended from 2015 to 2019

- **31 Dec 2017: CAD acceptance process closed**
  - 48 CADs from 22 sponsors
- **Dec 2017 – EWG reviewed 14 CADs with Final Study Report outcomes**
- **Nov 2018 – EWG reviewed 14 additional CADs with FSR outcomes**
- **2019**
  - Ongoing reviews by regulators and awaiting receipt of minimum 20 Category 3a/b cases
  - Regulators have requested a face-to-face regulator only meeting in early 2020
  - Goal is for entire EWG to meet in June 2020 to review entire study set

Table 1: Category designation by Sponsors and DRAs for CADs

	Sponsor	DRAs
Cat 1	3	3
Cat 2	13	20
Cat 3a/b	32	25
Total:	48	48

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

	Sponsor designation	DRA designation		
Category		Unanimous	Split	DRA Total
3a	15	7	6	13
3b	17	4	6	10
2/3a/3b	--	--	2	2
Totals:	*32*	*11*	*14*	*25*

efpia
European Federation of Pharmaceutical Industries and Associations

EFPIA ICH S1 Carcinogenicity Case Study Workshop

- 23 October 2019
- Sanofi, Paris

Table 3: CAD category designations of 28 reviewed studies

Category	Sponsor	DRAs
1	2	2
2	8	14
3a or 3b	18	12 (6 unanimous, 6 split)

F4 CAD & FSA Study Outcome

Drug: Cmpd X
CAD written month 19
First in Class

Target: Binds and stabilizes a circulating transport protein
Disease area: Neurological

Sponsor's position: Category 3b, tumors not expected in people or rats
(but left open possibility of rat-specific liver/thyroid tumors)

Basis for sponsor:

- Pharmacology: No evidence that target engages carci pathways (cell cycle)
- Genotoxicity: Not genotoxic by weight-of-evidence, but polyploidy observed
- Toxicology: No pre-neoplastic response in 26wk rat study up to 30mpk (~54x)
- Hormones: No effect on hormones at clinical dose
- Immunosuppression: None noted in standard tox studies
- Tg mouse study: 26wk HRas was negative

CASE 1

F4 CAD, EWG minutes

Code	Sponsor	DRA Post-TCON
F4	3B	2

PMDA, EMA, FDA

Basis for Category 2:

- First in class with an insufficiently characterized MOA
- Insufficient level of information on identification and exposure to metabolites was a concern, as their contribution toward the mild organ (kidney/liver) toxicity could not be addressed. Exposure multiples for metabolites could have been useful.
- Uncertain genotoxicity profile based on evidence suggesting possible aneugenicity and on limitations on dose selection for the genotoxicity studies performed.

CASE 1

FSA Study Outcome

2yr SD rats, 0, vehicle, 3, 10, 30mg/kg

Executive Summary

Sponsor & DRAs: Preliminarily negative for drug-induced tumors

Non-neoplastic findings:

Liver: Hepatocellular hypertrophy, multinucleated giant cells, foci of clear cell alteration

FSA-F4 Comparison
DRA Discussion

Why did DRAs differ from Sponsor?

- Cat 2 was largely based on lack of information (e.g., metabolite exposure, genetox) rather than a definitive for-cause concern of carcinogenicity.
- Lack of information precludes a confident prediction of Cat 3 and would result in Cat 2 again; however, such information likely obtainable in 'real' development.
- First in class issue remains even with added information (what defines a 'higher bar'?)

Did the study provide added value?

- Provided long-term carci data in rats for a 1st in class MOA, for both target and off-target activities

Final CAD numbers to support ICH S1 revision

Review of carcinogenicity study reports (as of 1 Feb 2021)

Parameter	n=
CAD-FSR* pairs reviewed	44
CAD-FSR pairs in house & to be reviewed	1
FSRs that will not be submitted	3
Remaining FSRs to be submitted	0
Total # CAD-FSR pairs expected	***45***
Cat. 3a/3b** CAD-FSR pairs reviewed	23
Cat. 3a/3b CAD-FSR pairs in house & to be reviewed	1
Cat. 3a/3b FSRs that will not be submitted	1
Remaining Cat 3a/3b FSRs to be submitted	0
Total # Cat. 3a/3b CAD-CSR pairs expected	***24***

FSRs that will not be submitted (n=3): P8 (DRA split cat. 2/3a), F26 (DRA cat. 2), F34 (DRA cat. 2)

*: Final study report

**: Category 3 cases are defined as those CADs where at least one DRA concurs with the sponsor that a 2 year rat study is not required to assess human carcinogenic risk

TESTING FOR CARCINOGENICITY OF PHARMACEUTICALS S1B(R1)

Step 2 document –released for comments

- **This document has been signed off as a Step 2 document (10 May 2021) to be issued by the ICH Regulatory Members for public consultation**
- **This document was developed based on a Concept Paper (14 Nov 2012) and a Business Plan (14 Nov 2012)**
- **This document is supported by scientific advances since S1B was adopted, several retrospective analyses of pharmaceutical datasets, and an independent international prospective study conducted by the ICH S1 EWG confirming that an integrated WoE approach could be applied to adequately assess the human carcinogenic risk for certain pharmaceuticals in lieu of conducting a 2-year rat study without compromise to patient safety.**
- **Anticipating finalization as a Step 4 document to be implemented in the local regional regulatory system: May / 2022**

Guideline Scope, Objectives, and Benefits

- **Scope:**
  - all small molecule pharmaceuticals where carcinogenicity evaluations are recommended as described in ICH S1A.

- **Objectives:**
  - Expand the testing scheme for assessing human carcinogenic risk by introducing an integrative approach that provides specific weight of evidence [WoE] criteria that inform whether a 2-year rat study would add value in completing a human carcinogenicity risk assessment.
  - Add a plasma exposure ratio-based approach for setting the high dose in the rasH2-Tg alternative mouse model.

- **Implications and Benefits**
  - Encourages a more scientifically based approach to carcinogenicity risk assessment of small molecules starting earlier in development.
  - Reduces the number of 2-year rat carcinogenicity studies with associated savings in animal use, costs and timelines.

Summary of Guideline Content (1)

- **An integrative WoE assessment approach as described in sections 2.1 and 2.2 may support a conclusion that the test compound is either:**
  - likely to be carcinogenic in humans such that the product would be labeled accordingly, and any 2-year rat carcinogenicity studies would not add value; or
  - likely not to be carcinogenic in humans such that a 2-year rat study would not add value (may also not be carcinogenic in rats, or may likely be carcinogenic in rats but through well recognized mechanisms known to be human irrelevant); or
  - uncertain with respect to the carcinogenic potential for humans, and a 2-year rat carcinogenicity study is likely to add value to human risk assessment.

Summary of Guideline Content (2)

- **Section 2.1: The WoE approach is based on a comprehensive assessment of the totality of data relevant to carcinogenic potential available from public sources and from conventional drug development studies, including:**
  1. data that inform carcinogenic potential based on drug target biology and the primary pharmacologic mechanism of the compound including carcinogenicity information available on the drug class,
  2. results from secondary pharmacology screens, especially those that inform carcinogenic risk,
  3. histopathology data from repeated-dose toxicity studies completed with the test agent, with particular emphasis on the long-term rat study including exposure margin assessments,
  4. evidence for hormonal perturbation,
  5. genetic toxicology study data using criteria from ICH S2(R1),
  6. evidence of immune modulation in accordance with ICH S8.

Summary of Guideline Content (3)

- **Section 2.2: While all factors contribute to the integrated analysis, the relative importance of each factor will vary depending on the specific molecule being considered.**
  - An established profile of other compound(s) in a drug class contributes substantially to assessing human carcinogenic risk associated with the drug target.
  - While compounds with novel drug targets (i.e., first-in-class) are considered eligible for an integrative WoE-based approach, a higher evidentiary standard is expected to establish no cause-for- concern.
  - Case Study examples are provided in Appendix 1 demonstrating how the WoE factors can be integrated in determining the need for a 2-year rat study.

Summary of Guideline Content (4)

- **Section 3: A plasma exposure (AUC) ratio for high dose selection in the rasH2-Tg model has not been globally accepted as an endpoint since the model was introduced under S1B.**
  - A comprehensive analysis of experience in the rasH2-Tg mouse model was completed and indicates that there is no value in exceeding a 50-fold plasma AUC exposure ratio (rodent:human) to support carcinogenicity assessment.
  - All criteria for selection of the high dose for carcinogenicity studies as specified in S1C(R2) for 2-year rodent studies are applicable to rasH2-Tg, including an AUC plasma exposure ratio, except that the exposure ratio will be 50-fold in rasH2-Tg rather than 25-fold as for 2-year studies conducted in wild type rodents.

Considerations

- **When the Sponsor's WoE assessment concludes that conduct of a 2-year rat study is not warranted, the Sponsor should seek alignment with the Drug Regulatory Agency [DRA] of each region where marketing approval is sought.**

- **When a Sponsor decides alternatively to conduct a 2-year rat study in accordance with ICH S1B, there is no obligation to seek concurrence nor to document their rationale with each DRA.**

- **A carcinogenicity study in mice, either 2-year or a short-term transgenic model as specified in ICH S1B, remains a recommended component of a carcinogenicity assessment except in unusual circumstances (e.g., only subtherapeutic pharmacologically inactive test exposures are achievable).**

Conclusions

- **S1B(R1) introduces a more scientifically based and integrated approach to assess the human carcinogenic risk for small molecule pharmaceuticals, using WoE criteria evaluated on a case-by-case basis in lieu of always conducting a 2-year rat study.**
- **A plasma exposure AUC ratio of 50-fold is an acceptable criteria for high dose selection for carcinogenicity studies in rasH2-Tg mice.**

THANK YOU

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Acknowledgements: The ICH S1B EWG and colleagues from IQ and EFPIA (especially Franck Sistare from Merck, Mike Graziano from BMS and John Valhe from Lilly) from whom I stole many slides ☺ !