



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

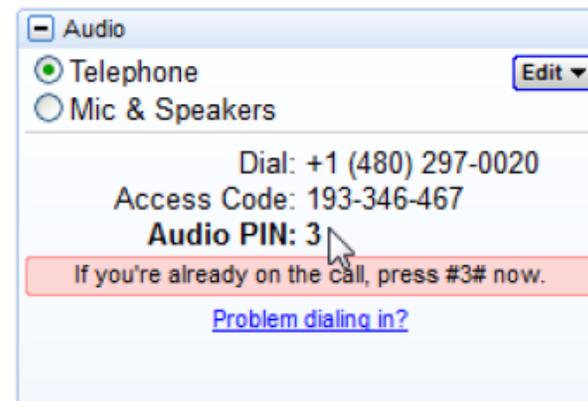
Agenda

- Brief introduction - Mike Graziano (Bristol-Myers Squibb)
- An overview of the ICH S1 project – Frank Sistare (Merck)
- Current status of CAD submissions - Todd Bourcier (FDA)
- A DRA perspective on a quality CAD – Abby Jacobs (FDA)
- Industry experience on preparing a CAD – Nancy Bower (Eisai)

Housekeeping

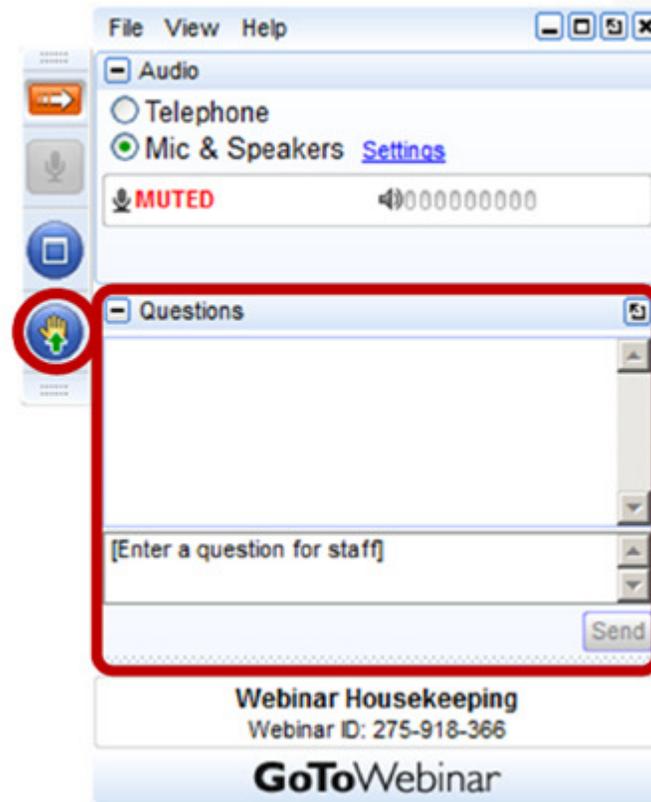
Your Participation

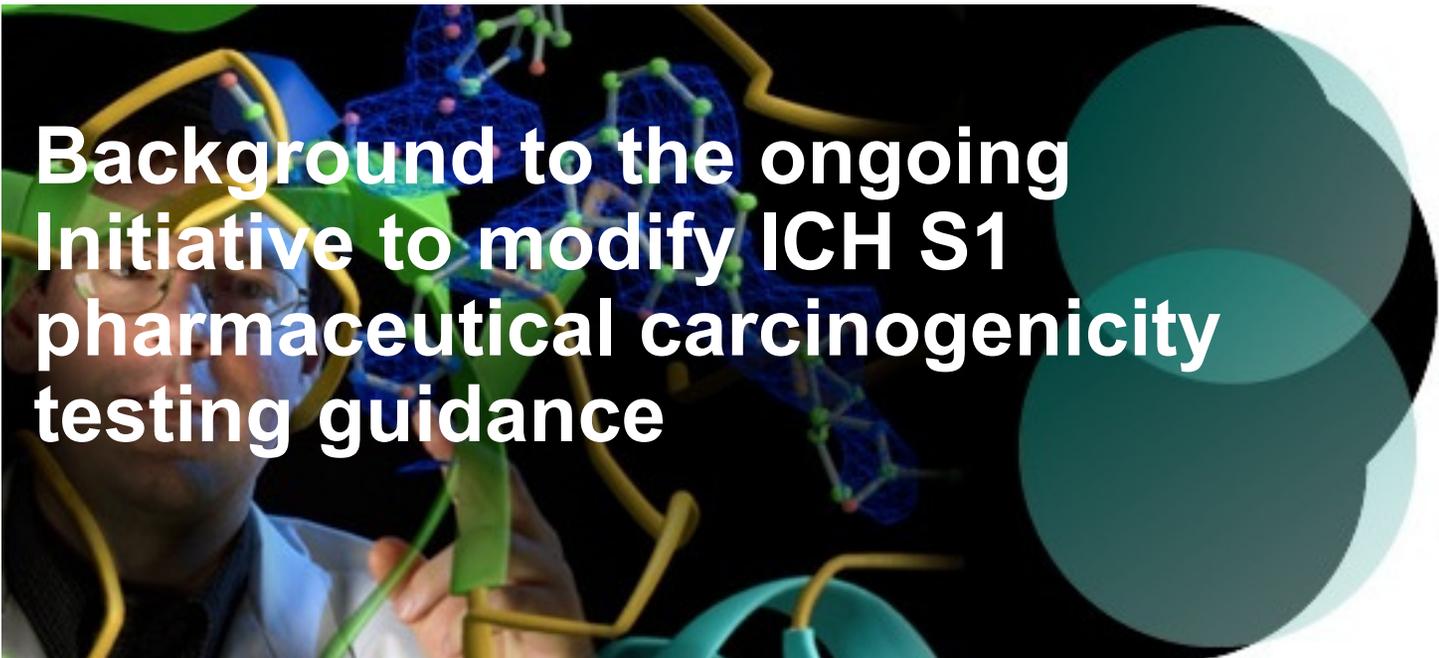
- If you have not done so already, please press #[Your Audio Pin]#
- **Note:** *Today's presentation is being recorded.*



Housekeeping

Submit written questions using the questions box.





Background to the ongoing Initiative to modify ICH S1 pharmaceutical carcinogenicity testing guidance

Frank D. Sistare

IQ Webinar
September 9, 2015



Recent publications have questioned the value of current 2-yr rodent testing practice

- 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
Copyright © 2011 by The Author(s)
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. SISTARE¹, DANIEL MORTON², CARL ALDEN³, JOEL CHRISTENSEN¹, DOUGLAS KELLER⁴, SANDRA DE JONGHE⁵, RICHARD D. STORER¹, M. VIJAYARAJ REDDY¹, ANDREW KRAYNAK¹, BRUCE TRELA⁶, JEAN-GUY BIENVENU⁷, SIVERT BJURSTROM⁸, VANESSA BOSMANS⁵, DAVID BREWSTER⁹, KARYN COLMAN¹⁰, MARK DOMINICK¹¹, JOHN EVANS⁸, JAMES R. HAILEY¹², LEWIS KINTER^{8*}, MATT LIU¹, CHARLES MAHRT¹³, DIRK MARIEN², JAMES MYER¹², RICHARD PERRY², DANIEL POTENTA¹⁰, ARTHUR ROTH², PHILIP SHERRATT¹, THOMAS SINGER^{9*}, RABIH SLIM⁹, KEITH SOPER¹, RONNY FRANSSON-STEEN⁸, JAMES STOLTZ¹⁴, OLIVER TURNER¹⁰, SUSAN TURNQUIST², MARJOLEIN VAN HEERDEN⁵, JOCHEN WOCKE¹¹, AND JOSEPH J. DEGEORGE¹

¹Merck 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.**
- **91% overall test sensitivity** w no human relevant misses among the 14 false negatives in the 266 chemical database.
- 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**



Be well

Starting with the end in mind

In the absence of evidence of pharmacological (e.g., hormonal), toxicological (e.g., genotoxicity and histologic risk factors), and any mouse (transgenic) tumor response, the 2 year rat bioassay provides little value in identifying potential carcinogenic risk.

In the presence of evidence of pharmacological, toxicological or mouse findings suggesting potential carcinogenic risk, the 2 year rat bioassay may provide information to clarify the level of risk.

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
- Proposal approved by ICH Steering Committee to form an ICH EWG to consider revision of S1 ICH Guidance and incorporating a requisite ***prospective data gathering approach*** and pharmacology assessment
- Regulatory Notice Document (RND) published on the ICH Website (Aug-2013) launching this prospective initiative

Regulatory Notice Document (RND) Posted to ICH Website Aug 2013 launching Prospective Evaluation

- http://www.ich.org/fileadmin/Punblic_Web_Site/ICH_Products/Guidelines/Safety/S1/S1_Regulatory_Notice_Document_8.Aug.2013.pdf

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.

Summary

- Expectation that a significant number of 2-year rat carcinogenicity studies could be omitted based on WOE criteria
- ICH S1 EWG efforts have been launched and a Regulatory Notice Document published (Aug-2013) launching prospective study period and providing CAD writing guidance
- It is critical that pharmaceutical companies submit CADs on all investigational drugs so the evaluation meets the requirement of minimum bias and contains diverse drug classes
- DRAs are reviewing CADs for sponsor predictions and actual outcomes
- Agreement between the sponsor and DRAs, and agreement between predictions and actual outcomes (approx. 50 studies) will determine whether S1 EWG will revise ICH S1 guidance for waivers of 2-yr rat studies



ICH S1 Prospective Evaluation Study Overview and Progress

T Bourcier and A Jacobs
CDER/FDA
Sept 2015

Study Overview and Progress

- Objectives of Study
- CAD submission & review
 - WOE evaluation and category designation
 - CAD = Carci Assessment Document
- 2yr Rat study submission & review
 - Comparison of actual study outcome to CAD predictions

Goal of S1 EWG

- Introduce a more integrated approach to address the cancer risk of small molecule pharmaceuticals.
- Define conditions under which 2-year rat bioassays add value/do not add value to carcinogenicity assessment

Objectives of Prospective Evaluation Study

- *Assess accuracy & value of WOE factors in predicting 2yr rat study outcome and value*
- *Assess concordance of decisions between Sponsors & Regulatory Agencies, and among Regulatory Agencies across regions*



Participating Drug Regulatory Agencies (DRAs)

➤ ***FDA, EMA, PMDA, HC***

HC fully participating in PE Study since March 2015

CAD submission & review

Sponsor



- *Submits CAD*
- *RND Guidelines*

Primary DRA



- *CAD is coded, screened*
- *Anonymized document*
- *Written $\leq 18m$ of ongoing rat study*
- *Completed Template*

Distributed to DRAs

- *Blinded to Sponsor ID*
- *Reviews & designates Category independently*

CAD submission & review

DRAs meet by t-con periodically



- *Each presents category & rationale*
- *Agreement/Disagreements discussed*
- *Consensus reached when possible*
- *Categories pre/post-discussion recorded*

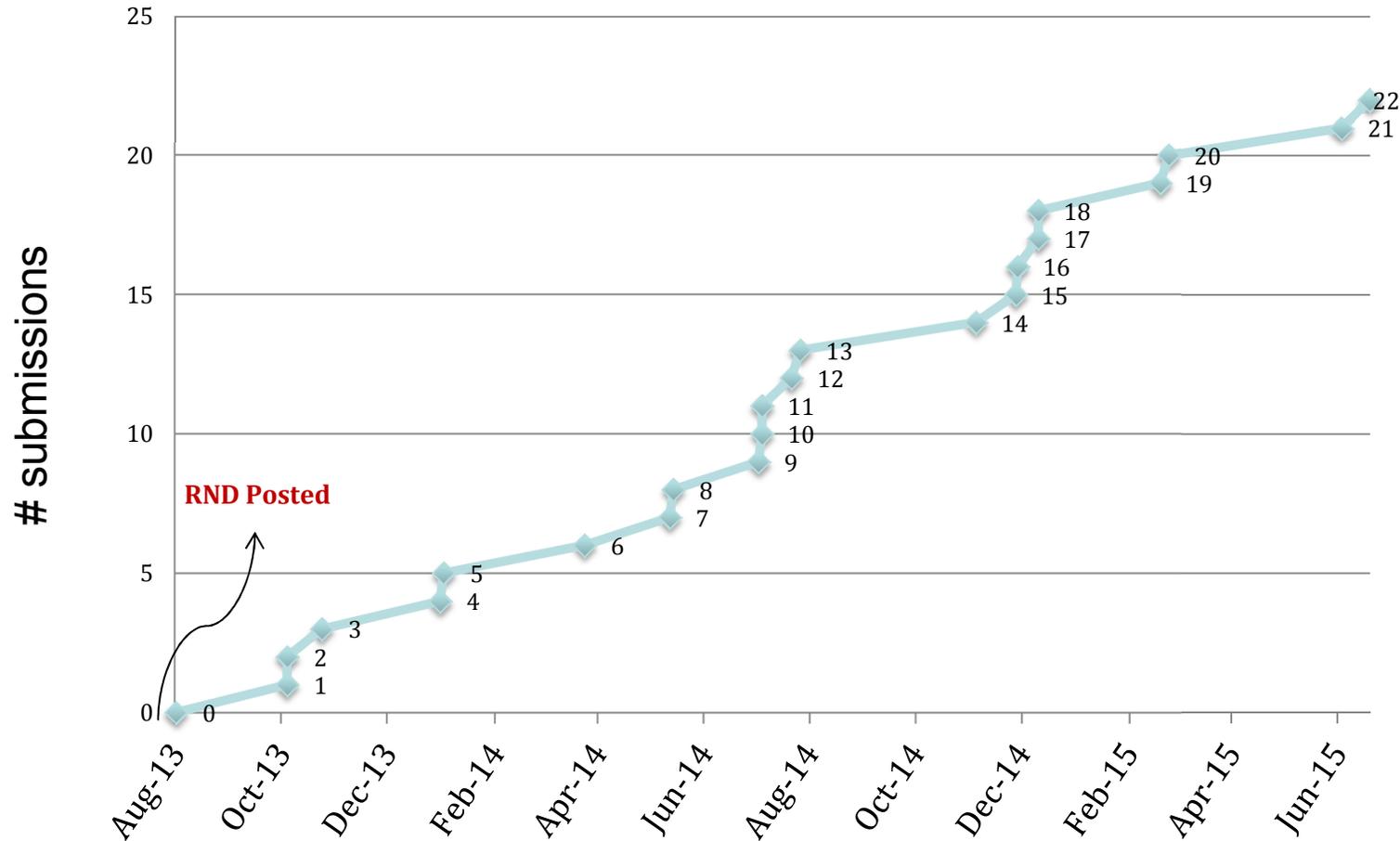
Feedback sent to sponsor

(if requested)

- *Sent by primary DRA*
- *Provides DRA's consensus category w/ brief rationale*

Participation

CAD Submissions, Aug 2013-15 (Cumulative)

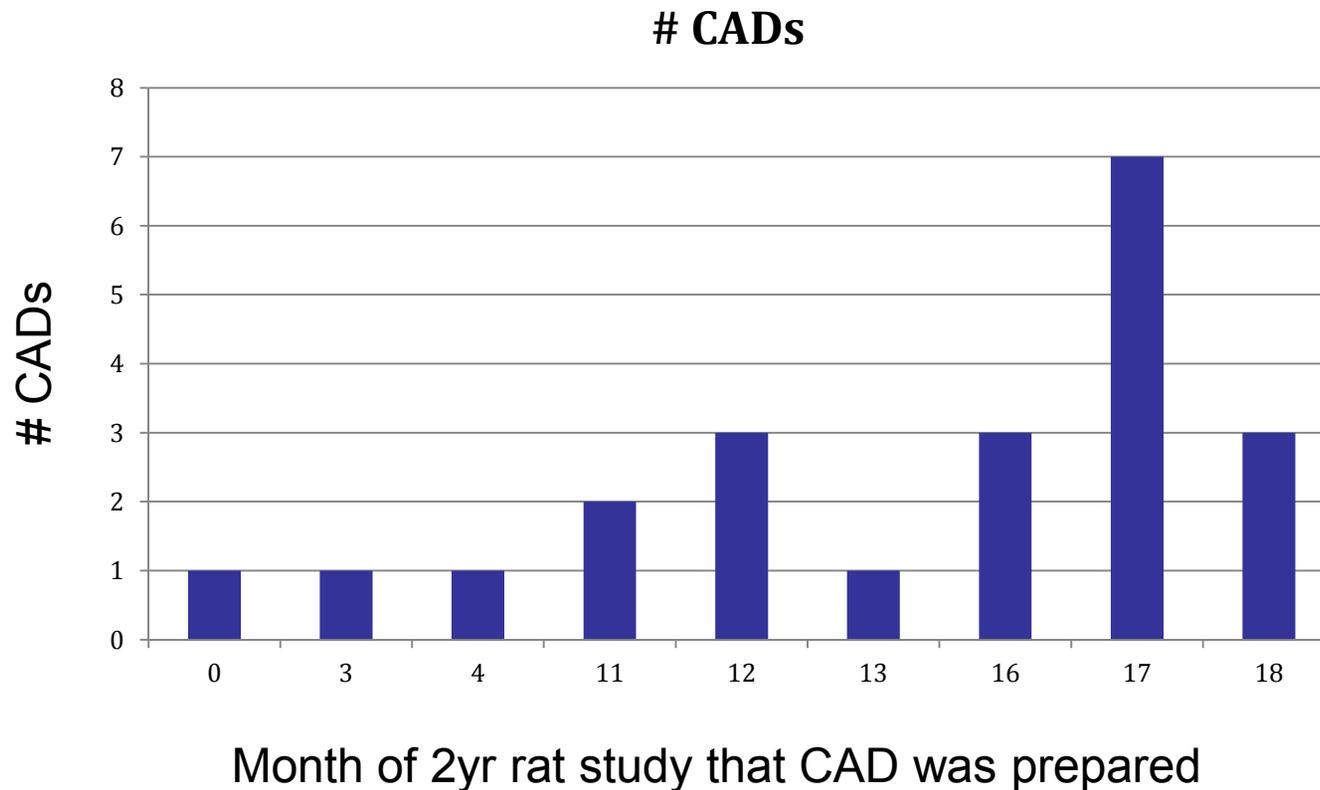


✓ **11 sponsors submitted 18 CADs to FDA (as primary DRA)**

Participation

Dosing in the 2-yr rat carci studies should not have exceeded 18-month duration to minimize potential for bias. It is encouraged that CADs be authored prior to or within the first 12 months of initiation of dosing.

–RND (2013)



Participation

- ✓ FDA received ~73 rat carci protocols, Sept 13-Aug 15
- ✓ Estimated ~25 ongoing rat carci studies in 2013/14
- ✓ This estimate does not include programs in non-US regions

- *Many more programs can contribute to this effort*
- *Broader participation highly encouraged!*
- *Particular interest in CADs written $\leq 12m$ of ongoing rat carci study*

Categories & Concordance

	Sponsor	DRAs	Concordance	
			Sponsor/DRAs	DRAs
Cat 1	1	0	0	0
Cat 2	5	12	3	5
Cat 3a	8	5	5	5
Cat3b	6	1	1	1
Undecided	0	2		

Cat 1: Human risk, no rat study

Cat 2: Not predictable, rat study adds value

Cat 3a: Rat tumors predicted by human-irrelevant MOA; rat study would not add value

Cat 3b: No rat or human risk, rat study would not add value

Interim Trends

➤ DRAs agreed with 6 of 14 proposed Cat 3 CADs

- ✓ *Pharmacologic MOA*
- ✓ *Toxicological profile*
- ✓ *Drug 'class' profile*
- ✓ *Known tumorigenic MOAs (in rodents)*
- ✓ *Supportive Literature*

➤ DRAs selected Cat 2 for 7 of 14 proposed Cat 3 CADs

Less confidence in risk prediction for rats/humans

- ✓ More risk-averse interpretation of data
- ✓ Scant information on drug target (e.g., first in class)
- ✓ Multiple drug targets (intended or not)
- ✓ Insufficient description of key information
- ✓ Omission of key literature
- ✓ Incomplete discussion of relevant tox findings

2yr Rat study submission & review

Comparison of actual study outcome to CAD predictions

- One (1) summary report of final 2yr rat study submitted
- Tumor incidence Tables will be critical
- Pending review & discussion by DRAs

Summary & Conclusions

- ✓ Prospective study is in data-collection phase
- ✓ Broader participation critical for reaching goals
- ✓ Cases of concordance and non-concordance will prove equally useful in guiding direction of S1 EWG



What is a High Quality Carcinogenicity Assessment Document (CAD)?

A. Jacobs and T. Bourcier
CDER/FDA
9/2015

Goal

- Define conditions under which 2-year rodent bioassays add value/do not add value to carcinogenicity assessment

Organization of CAD

- It helps to have the template as the cover page :
- Sponsor does or does not wish to receive feedback from reg authorities
- Predicted outcome from 2-yr rat study
- Projected value to carc assessment and human risk implications
- Categorical assignment and risk assessment
- Other boxes in the cover page will be filled out after carc results are received

Template for Use in Submitting Carcinogenicity

Assessment Documents

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

<i>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.</i>		
Tumor Outcome from 2yr Rat Carcinogenicity Study		
Prediction by Sponsor	Actual Outcome According to Sponsor	
	Actual Outcome According to DRA	
Value to carcinogenicity assessment and human risk implications		
Projected Value	Actual Value	
Categorical Assignment and Waiver Request		
Predicted Category by Sponsor	DRA Concurrence (Y/N) Predicted Category	Actual Category
Waiver requested (Y/N)	Waiver supported (Y/N)	Waiver supported (Y/N)

Categories (a)

- *ICH posting:*
<http://www.ich.org/products/guidelines/safety/article/safety-guidelines.html>
- Category 1—so likely to be tumorigenic in humans that a product would be labeled as such, and a 2-year rat study would not add value;
- Category 2—the available sets of pharmacologic and toxicologic data indicate that tumorigenic potential for humans is uncertain, and a 2-year rat study is likely to add value to human risk assessment;

Categories (b)

- Category 3a— likely to be tumorigenic in rats but not in humans through prior-established and well-recognized mechanisms known to be human irrelevant that a 2-year rat study would not add value; or
- Category 3b— likely not to be tumorigenic in either rats or humans that no 2-year rat study is needed.

It helps to have a table of contents

- Summary of analysis: half page
- Background material:
- Metabolism- across species
- Pharmacology- drug target, receptor binding screens, pathways, secondary pharm
- When there is no endogenous target for the drug
- Carc results with other drugs with similar pharmacol: relevance to humans or rat-specific?
- Genetox results

Other Considerations

- Histopathology in organs in tox studies of increasing length:
- Rats, nonrodents, transgenic mouse carc study
- Exposure margins relative to humans in tox studies
- Hormonal perturbation
- Immunosuppression
- Special studies and endpoints

Discussion and Conclusions

- Reasons for category selected
- References

What makes a Quality CAD?

- Appropriate covering of relevant literature- sometimes not complete
 - With regard to human relevance of pathways
- Good Integration of all the material to reach a conclusion
- Well written
- The logic is easy to follow

First

- Take a look at The ICH Regulatory notice document appendix 1, which presents WOE factors for consideration in a CAD and describes each element
- Then if not sure about something,
- Ask! Send queries to FDA-CAD@fda.hhs.gov

Secrets to a Successful CAD Submission: The Eisai Experience

Nancy Bower
Senior Director, Global Regulatory Affairs - Nonclinical
Eisai Inc

Disclaimer

- ◆ The views and opinions expressed in the following presentation are the personal views of the individual presenter and do not necessarily represent the views of the company at which she is employed.

Outline of the Presentation

- ◆ Introduction
- ◆ Timelines
- ◆ CAD Structure
- ◆ Outcomes
- ◆ Keys to Success
- ◆ Conclusions

Introduction

- ◆ COMP A is a new chemical entity for which a 2-year rat carcinogenicity study is currently ongoing
- ◆ Increased liver weights, induction of CYP3A, and hepatocellular hyperplasia were noted in the rat toxicity studies conducted with COMP A
- ◆ Hepatocellular tumors and thyroid follicular tumors resulting from a rodent-specific mechanism were projected as a possible result of the 2-year rat carcinogenicity study
- ◆ In the CAD submitted in Feb 2015, Eisai predicted COMP A as a Category 3A drug*

* 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

Timelines



*Note: Because of competing project work, resources were not fully dedicated to the preparation of the CAD

GRA-NC = Global Regulatory Affairs - Nonclinical

CAD Outline

- ◆ TOC
- ◆ Template for use in submitting carcinogenicity assessment documents
- ◆ Summary
- ◆ Background information on COMP-A
 - ◆ Pharmaceutical class
 - ◆ MOA
 - ◆ Information about other approved drugs in the class (n=1)
 - ◆ Regions where approved, summary of key genotoxicity and carcinogenicity data, including exposure multiples and tumors observed
- ◆ Individual chapters on the weight-of-evidence factors for consideration as outlined in the RND
- ◆ Conclusion
- ◆ List of references

CAD Structure

- ◆ CAD was structured to give Eisai confidence that all necessary information was included and key points were addressed
 - ◆ CAD structure was driven by the information in Appendix 1 of the Regulatory Notice Document (RND)
 - ◆ Individual chapters for all of the weight-of-evidence (WOE) factors were included
- ◆ The “Template for Use for Submitting Carcinogenicity Assessment Documents” in Appendix 2 was provided at the beginning of the CAD as a summary of key information and Eisai’s categorization of its drug
- ◆ Final CAD, including cover page and summary template was 16 pages long

Weight-of-Evidence Criteria

Discussion in the CAD - 1

- ◆ Knowledge of intended drug target and pathway pharmacology, secondary pharmacology, and drug target distribution in rats and humans
 - ◆ Very high level summary of in vitro and in vivo pharmacology
 - ◆ Review of secondary and off-target pharmacology including potential relevance to humans and discussion of carcinogenic risk associated with off-target pharmacology
 - ◆ Drug target distribution in rats and humans
 - ◆ Noted the lack of available information for human genetic polymorphisms in the target or pathway and targeted genomic biomarkers
- ◆ Genetic study results
 - ◆ Results of the genetic toxicology study battery with COMP A
 - ◆ In silico analysis with 3 possible major metabolites
 - ◆ Ames Test results for 1 possible genotoxic impurity (GTI)

Weight-of-Evidence Criteria Discussion in the CAD - 2

- ◆ Results of histopathologic evaluation of repeated-dose rat toxicology studies
 - ◆ 4-week rat study
 - ◆ Increased liver weights, hepatocyte hypertrophy, P450 induction confirmed by immunohistochemistry
 - ◆ 13-/26-week rat study
 - ◆ Increased liver weights, centrilobular hepatocellular hypertrophy, thyroid follicular cell hypertrophy
- ◆ Evaluation of histopathologic risk factors in the rat chronic toxicity study
 - ◆ Discussion of liver and thyroid changes, with supporting information from the literature discussing human relevance
 - ◆ No evidence of hyperplasia in other tissues
- ◆ Exposure margins in the chronic rat toxicology studies
 - ◆ Table correlating noteworthy findings at each dose level in the 26-week rat toxicity study to the systemic exposure based on AUC and the multiple of the human exposure at the highest anticipated human dose

Weight-of-Evidence Criteria Discussion in the CAD - 3

- ◆ Metabolic Profile
 - ◆ Discussion of the binding affinity of the one major metabolite for the pharmacologic target
 - ◆ Table summarizing multiples of the human exposure at the highest anticipated human dose
- ◆ Evidence of Hormonal Perturbation
 - ◆ Discussion of drug-related effects on ACTH and gonadotropic hormones to potentially be associated with carcinogenesis
- ◆ Immune Suppression
 - ◆ Noted lack of evidence of immune suppression in both rats and the nonrodent species

Weight-of-Evidence Criteria

Discussion in the CAD -4

- ◆ Results of Non-Rodent Chronic Studies
 - ◆ Summarized and discussed the relevance to humans of the findings in both the 13- and 39-weeks studies that might suggest a carcinogenic risk
- ◆ Special Studies
 - ◆ Special studies conducted to determine the mechanism of toxicity for findings observed in the 13-/26-week study
 - ◆ Relevance of these findings to carcinogenic risk discussed with supporting information from the literature
- ◆ Genetically Engineered Rodent Models
 - ◆ Provided information about knock-out models and the lack of findings related to carcinogenicity in these models

Outcome

- ◆ CAD submitted late Feb 2015
- ◆ Reviewed during the next DRA review cycle
- ◆ Eisai notified June 2015 that the DRAs agreed with Eisai that COMP A should be categorized as Category 3A

Keys to Success - 1

- ◆ Applying lessons learned by other companies
 - ◆ Review team members are members of the PhRMA S1 LD-KIT and IQ DruSafe and were able to share lessons learned by other companies
 - ◆ Application should be anonymous
 - ◆ Providing supporting literature and information for compounds in the same class for the assessment of carcinogenic risk associated with all findings
- ◆ Allowing ample time to complete the CAD
 - ◆ Recognizing and planning for competing priorities that would affect timelines for completion

Keys to Success - 2

- ◆ Thoroughly addressing each of the weight-of-evidence criteria
 - ◆ Identifying and addressing all findings in the rodent studies of possible relevance to the assessment carcinogenic risk
 - ◆ Providing supporting information from the literature and where available, other compounds in the class
 - ◆ Identifying and acknowledging factors for which no data is currently available
 - ◆ Human genetic polymorphisms in the target or pathway
 - ◆ Targeted tissue genomic biomarker measurements

Keys to Success - 3

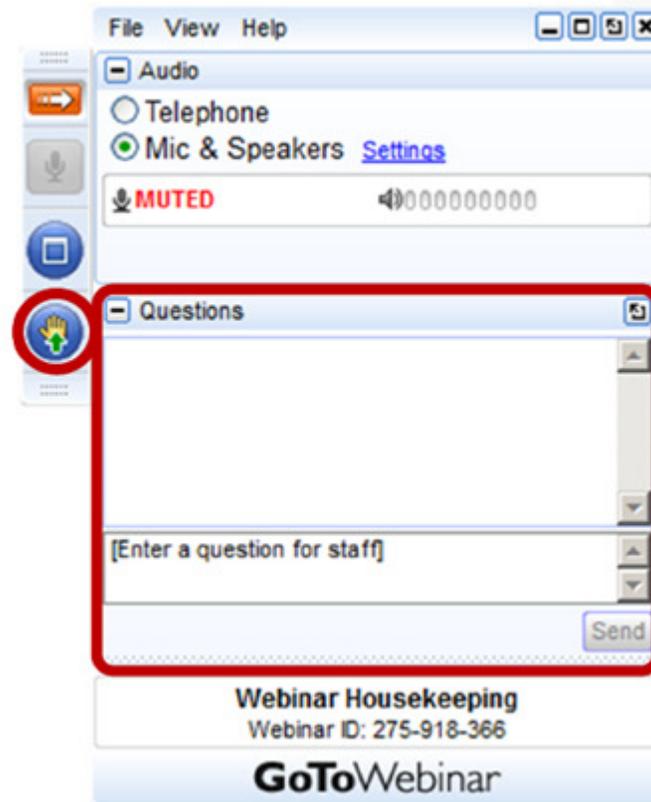
- ◆ Providing a thorough literature review and discussion of the human carcinogenic risk associated with off-target pharmacology
- ◆ Supporting our position on the lack of human relevance of histopathologic changes seen in the rodent studies with appropriate information from the literature
- ◆ Providing information from the literature to support our position that the anticipated neoplastic changes in the 2-year rat study would be the result of a rodent-specific mechanism

Conclusions

- ◆ Preparation of a CAD is a straightforward, stepwise process
- ◆ Keys to success include:
 - ◆ Proper planning
 - ◆ Addressing all WOE criteria
 - ◆ Being thorough and providing supporting information from the literature
 - ◆ Applying the lessons learned by others and shared today

Housekeeping

Submit written questions using the questions box.





INTERNATIONAL CONSORTIUM *for*
INNOVATION & QUALITY
in PHARMACEUTICAL DEVELOPMENT

Thank you for attending the
webinar!