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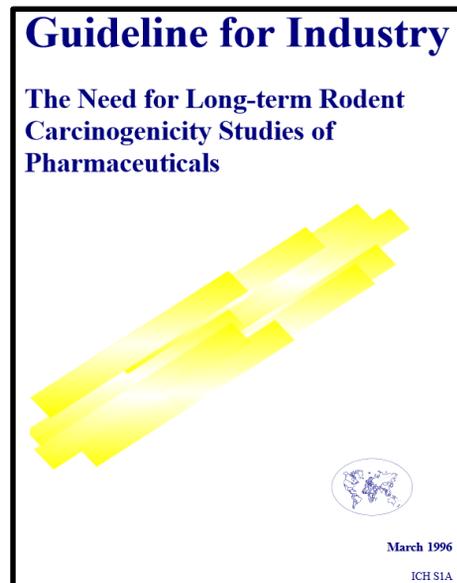
WEIGHT OF EVIDENCE APPROACHES FOR EVALUATING CARCINOGENESIS IN DRUG DEVELOPMENT

APRIL 29, 2019

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Regulatory Framework for Carcinogenicity Assessment: International Council for Harmonisation (ICH) Guidances

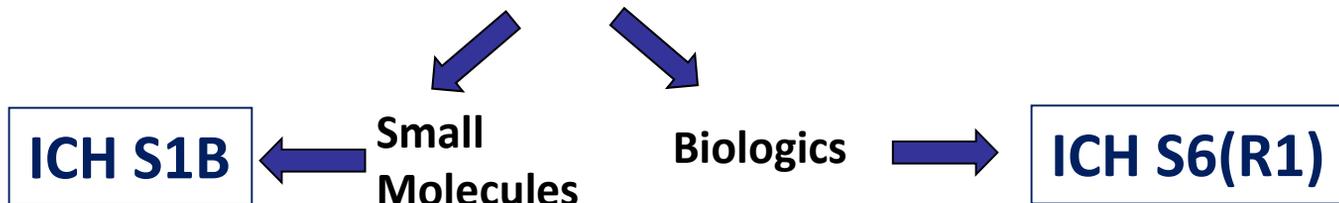
- **S1A:** The need for long-term rodent carcinogenicity studies of pharmaceuticals
- **S1B:** Testing for carcinogenicity of pharmaceuticals
- **S1C(R2):** Dose selection for carcinogenicity studies of pharmaceuticals
- **ICH S6(R1):** Preclinical safety evaluation of biotechnology derived pharmaceuticals
- **M3(R2):** Nonclinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals



When is a Carcinogenicity Assessment (CA) Needed?

Factors influencing need/timing for studies:

- *Treatment Duration: ≥ 6 months*
- *Cause for Concern*
- *Genotoxicity*
- *Patient Population/Indication*



Assessment Strategy Under ICH S1B

ICH S1B: ‘A “weight of evidence approach” ... enhances the assessment of carcinogenic risk to humans’

- One long-term rodent carcinogenicity study (default is rat)
- One supplemental study that provides additional information
- When applicable, mechanistic studies addressing relevance of observed tumors

Supplemental study?

- Short/medium term *in vivo*: Transgenics ... but also promoter models, neonatal studies, mechanism driven studies
- Long-term carcinogenicity study in second rodent species

Study Review: Evaluation of Results

- Histologic evaluation is the primary basis for identifying drug-related effects
- Complete set of tissues evaluated microscopically
- In many tissues, there is a continuum of effects from hyperplasia to adenoma to carcinoma
 - Evaluate benign and malignant findings separately and combined when considering drug-relatedness
- Some toxicities can obscure neoplastic changes
 - Severe chronic nephropathy (kidney)
 - Mononuclear cell leukemia (liver)

Study Review: Evaluation of Results

- Evaluation involves both toxicologists and statisticians
- CDER statisticians evaluate each study that is submitted
- Tests may include
 - Trend test—incidence in all groups simultaneously
 - Pairwise test—compare each group individually
 - Time adjusted (for survival) and unadjusted tests

Risk Assessment Considerations

- Genotoxicity data—relevance to *in vivo* human use
- Strength of evidence for carcinogenic hazard
- The frequency, duration, and intensity of exposure of humans to the drug
- Non-neoplastic effects, mode of action data, other relevant data
- Formal numerical risk assessments are not conducted for pharmaceuticals

Relevance of Results?

~ 50% of two-year bioassays are positive in one or both test species (Van Oosterhout et al., 1997)

Strength of evidence considers:

- Findings in multiple organs
- Findings observed across multiple species or strains
- Findings observed in males and females
- Magnitude of increased incidence
- Dose-related trends
- Degree of malignancy
- Historical control incidence and rarity of finding

Assessment Strategy Under ICH S6(R1)

ICH S6(R1):

- Sponsor should design strategy to address potential hazards
- WOE composed of *'relevant data from a variety of sources'*
 - Target biology (genetic, disease models, etc.)
 - Class effects
 - In vitro studies
 - Toxicology studies
 - Clinical studies

Guidance for Industry

S6 Addendum to Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

May 2012
ICH

Assessment Strategy under S6(R1)

What does the WOE support?

Clear Risk



'Rodent bioassays are not warranted'
Address with label and risk mitigation

No/Low risk



Additional nonclinical testing not needed

Unclear risk



Sponsor needs to propose additional studies to address concerns
(i.e., mechanism-based studies, rodent bioassays)

Assessment Strategy for Biologics

- ✓ **Target-specific:** No substantial off-target activity
- ✓ **ADME simpler:** Reactive metabolites unlikely
- ✓ **High Human specificity:** Rodent studies sometimes just aren't feasible (e.g., no activity, neutralizing ADA)

But the S6 WOE approach is applicable, even if rodent studies are feasible

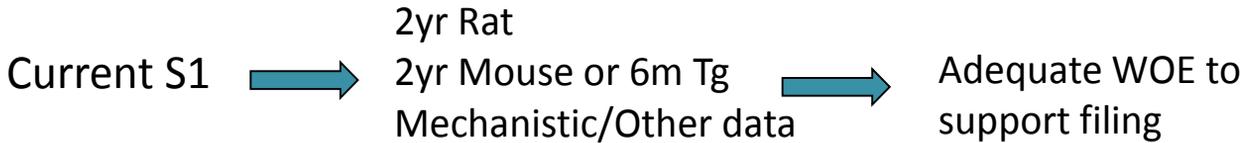
Recognition that the carcinogenic potential of biologics can sometimes be reasonably predicted based on a WOE approach, **without the need for a two-year rodent bioassay**

ICH S1 Expert Working Group Discussing an ‘S6-Like’ Approach to CA for Small Molecules

Limitations of two-year rodent study well-documented, alternatives long-sought:

- Positive results common and are often found or known to be irrelevant to the therapeutic use of the drug
- Resource intensive: animal usage, expensive, and time-consuming
- Alternative proposals seek to eliminate or shorten the two-year bioassay, by *predicting* tumor outcome from short-term toxicity studies

Proposed Change to ICH S1 Guideline



Potential option

Carci Assessment Doc
for cases where existing data already supports negligible or likely carci risk

Regulatory Review

Disagree

Follow standard assessment

Agree

Rat study waived
2yr mouse or Tg conducted

ICH S1 EWG Approach Update

Prospective Evaluation Period necessary to guide EWG's next steps in addressing S1 guidances

2012 'Regulatory Notice Document':

- **Voluntary call for submission of 'virtual' Carci Assessment Documents (CADs) for all ongoing/planned two-year studies**
<http://www.ich.org/products/guidelines/safety/article/safety-guidelines.html>

Objectives

- 1. Assess accuracy & value of predicted vs. actual two-year rat study outcome**
- 2. Assess concordance between Sponsors & DRAs, and among DRAs across regions**
- 3. Define criteria where a CAD WOE is an option to a two-year rat study**

Considerations in Preparing a WOE CAD

The following should be addressed, as warranted:

- *Target assessment & Drug selectivity*
- *Genetic toxicology*
- Histopathology & Exposure margins from chronic rat toxicology study
- Hormonal perturbation
- *Metabolic profile*
- Immune suppression
- Nonrodent chronic study results
- Transgenic studies
- Special studies & endpoints

- *Which will prove most useful/persuasive? Which is the least?*
- *Are data sufficient to predict outcome of the two-year rat study and adequately address the drug's carcinogenic potential?*

Sponsors and DRAs Categorize CADs

Based on WOE, Sponsors and DRAs independently categorize compounds:

➤ **Cat 1**

Predicted human carcinogen; no need for additional animal studies

➤ **Cat 2**

Cancer risk is uncertain, rodent bioassays *will* add value

➤ **Cat 3a**

Tumors predicted in rats, but by species-specific, human irrelevant pathway

➤ **Cat 3b**

Predicted cancer risk is low or absent for both rats and humans

Conclusions

- Weight of evidence approaches differ between traditional small molecule pharmaceuticals and biopharmaceuticals.
- An ICH working group is conducting a prospective study to evaluate whether a WOE approach similar to that used for biopharmaceuticals can be applied to small molecule pharmaceuticals to reduce the need for traditional 2 year rat studies.

Acknowledgements

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